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Return to Howard

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Editor
ROY WALDO MINER

ORAL FAT EMULSIONS

BY

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Consulting Editor, F. J. STARE

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ORAL FAT EMULSIONS*

Consulting Editor, FREDRICK J. STARE

CONTENTS

Introduction to Oral Fat Emulsions. *By* FREDRICK J. STARE 3
The Importance of Fat in the Diet. *By* R. W. SWIFT .... [illegible]
Fat Absorption and the Experimental Basis of Oral Fat Emulsions. *By* ROBERT P. GEYER 16
Clinical Studies on the Use of an Oral Fat Emulsion. *By* MILTON SHOSHKES 22
Oral Fat Emulsions in the Study of Calorie-Nitrogen Relationships in Man. *By* THEODORE B. VAN ITALLIE, FRANCIS D. MOORE, and FREDRICK J. STARE 28
Oral Fat Emulsions in the Feeding of Patients with Severe Burns. *By* STANLEY M. LEVENSON, ELIZABETH A. LOUNDS, and ROSALYN MORRIS 37
Fat Ingestion and Chylomicrons. *By* H. NECHELES 46
The Use of Oral Fat in Hyperalimentation and Parenteral Alimentation. *By* ANTHONY A. ALBANESE 55
The Use of Oral Fat Emulsions in Experimental and Clinical Medicine. *By* ARTHUR GROLLMAN 65
The Use of Oral Fat Emulsions in Surgical Patients by Mouth, Gastrostomy, and Jejunostomy—Clinical and Metabolic Studies. *By* IRVING F. STEIN, JR., W. JAMES KUHL, JR., EDWARD M. GOLDBERG, MORTON I. GROSSMAN, and KARL A. MEYER 69
The Use of an Oral Fat Emulsion in the Supportive Treatment of Pulmonary Tuberculosis. *By* MORRIS E. DAILEY 77
Experimental Studies in Human Gastric Physiology—I. The Effect of Fat upon Gastric Evacuation after Partial Gastrectomy. *By* W. R. WADDELL, and C. C. WANG 83
Absorption of Orally Administered Emulsified Lipid in Pancreatic Insufficiency in Infants and Children. *By* CHARLES U. LOWE, and CHARLES D. MAY...... 93
Oral Fat Emulsions Combined with Protein Supplements in the Management of Acute Poliomyelitis. *By* GEORGE J. BOINES 99
Laboratory and Clinical Studies Following the Use of an Oral Fat Emulsion. *By* S. D. JACOBSON 104
Forced High-Caloric Low-Protein Diet in the Treatment of Uremia. *By* W. J. KOLFF 107
Importance of Calories in the Growth of Children. *By* ICIE G. MACY 122
Interrelationships of Foodstuffs. *By* JOHN P. PETERS 127

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* This series of papers is the result of a Conference on *Oral Fat Emulsions and Their Use in Medicine* held by the Section of Biology of The New York Academy of Sciences, April 29, 1952.

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INTRODUCTION TO ORAL FAT EMULSIONS

By Fredrick J. Stare

Professor of Nutrition and Chairman of the Department of Nutrition, Harvard University, Boston, Mass.

Undernourishment may be almost as much of a medical problem as overnutrition. In the usual interpretation of these terms, we are thinking of weight and calories.

Realizing that there are many sick people who have lost weight, are losing weight, and are unable to eat adequately for a variety of reasons, we have been actively engaged for a period of ten years in developing emulsions of fat that can be given by vein and by mouth to supply an abundance of calories.

This monograph deals with oral fat emulsions and their use in medicine. The oral fat emulsions we have developed have varied from 40 to 50 per cent fat and 5 to 10 per cent glucose.

It is important that the emulsion be of very fine particle size, not because of improved absorption in the person with normal gastric and pancreatic secretion, but to improve the acceptance or palatability of the emulsion.

Our interests were increased and maintained when we found that we could put weight on individuals with tuberculosis, cancer, and other emaciating diseases who had continually lost weight, something we had been unable to do with ordinary food.

THE IMPORTANCE OF FAT IN THE DIET*

By R. W. Swift

The Pennsylvania State College, State College, Pa.

The use of fats by man dates back to prehistoric time. Their use as food was probably instinctive, but their other applications were apparently brought about as a result of observation of their properties and behavior under various environmental conditions. It is known that the Egyptians used olive oil as a lubricant and that axle greases consisting of a fat and lime along with other materials were used in lubricating Egyptian chariots as early as 1400 B.C. Soap has been known for 2000 years, and the use of fats and oils in the arts, in technology, and in medicine during this period of time is shown by ancient records.

During the past 25 years, the interest and research concerning fats and fatty acids has rapidly and steadily increased. Many derived products have been found to possess characteristic properties which adapt them to a variety of special uses such as detergents, weed killers, insecticides, wetting agents, cosmetics, plastics, impregnating and finishing agents for textiles and leather, and many other uses. This demand for fats constitutes a serious economic competition for the use of fats as food.

From a broad point of view, there is no nutritional requirement for fats or carbohydrates corresponding to that for the amino acids comprising the proteins. The normal person can fare equally well on a diet relatively high or low in either fat or carbohydrate. The energy requirements of the body can be met by a combination of fat and carbohydrate in widely different proportions, but the formation of fat from carbohydrate in the animal body does not mean that no fatty acids are required in the diet. It has been shown that arachidonic, linoleic, or linolenic acids must be supplied in the food. The human requirement is apparently small, and since these acids are found in many food oils as well as in egg yolk, and in the organs and tissues of animals, an adequate intake from the average diet is assured.

The process of normal fat oxidation seems to require the presence and oxidation of a small amount of carbohydrate. Of all the peoples of the world, the only group which may be suspected of consuming more fat than is compatible with optimum nutrition is the Eskimo.

Any one who has consumed a fat-free experimental diet can appreciate the importance of the satiety value of dietary fat. Apart from any other consideration, this contribution of fat to a diet is of great practical importance. It is interesting to note in this connection that sheep, although unaccustomed to rations of high fat content, have been found to consume, with apparent relish, experimental rations made to contain 9.8 per cent of fat by the addition of corn oil.[14]

Fat consumption *per capita* varies widely with food habits, but any drop below the usual level causes discontent. Dietary fat may thus be considered to have definite morale value. Though the subject of normal and excessive body fat hardly falls within the scope of this paper, brief mention may be made of the fact that the fat stores of the body represent the chief stockpile of energy which may be drawn upon when needed. Body fat also acts as a protector and support to vital organs and is important in the regulation of body temperature. The formation of body fat from dietary carbohydrate is common knowledge. In his recent book,[12] Dr. E. S. Nasset remarks that "every farmer knows that a pig can convert large quantities of starch into fat. A great many humans have discovered to their consternation that they also have this ability in common with the pig."

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Competition for the use of fats in the manufacture of various industrial products is very keen. The fat content of rations for livestock has been reduced to a low level by developments in solvent extraction, whereby oil meals may contain only a fraction of one per cent fat. It is evidently more profitable to extract and sell the oils, as such, rather than to leave them in the meals as a part of the feed.

Definite evidence that fat or specific fatty acids may be indispensable in the rations of farm animals is lacking, but this is not to be construed to mean that fat is of no importance in the rations of livestock. On the contrary, Maynard and associates at Cornell University have shown in extensive experimentation with dairy cattle over a period of many years that fat in the ration is essential for optimum milk production. Rations low in fat resulted in a lessened milk production with a tendency toward a lower fat content. They concluded that a concentrate containing four per cent fat is satisfactory if fed with good roughage.

In general, fats are highly digestible. The digestibility of fats with short-chain fatty acids and with low melting points may be as high as 97 per cent, while the digestibility of mutton fat with a melting point of 50°C. is about 88 per cent. From the standpoint of furnishing available energy to the body, fats occupy a special position among the foodstuffs. On a weight basis, fats are in this respect about two and a quarter times more effective than either protein or carbohydate. This fact may be of prime importance in cases in which an energy supply to the body is a critical factor. Other papers on the program will deal with this important aspect of fat metabolism.

Students of energy metabolism have long been interested in the increase in heat production which results from the ingestion of food. This specific dynamic effect or heat increment is an unavoidable waste incident to food utilization. The precise mechanisms involved are unknown. An exhaustive amount of work dealing with the dynamic effect of protein, carbohydrate, and fat has been reported during the past fifty years. I should like to evaluate critically the procedures and experimental conditions imposed in much of this work, and to present data showing that fat in the diet results in a more economical use of the energy of the entire diet.

Many of the earlier experiments with humans and experimental animals were of the "spot-check" type, with which a measure of the peak of the metabolism was sought rather than the total area under the curve, so that the total expense of utilization was not determined. The height of the metabolism may bear no particular relation to the entire heat increment. Furthermore, much of this work was done by comparison of the heat production of the fasting subject with that following the ingestion of either protein, fat, or carbohydrate. To ascribe the increase in metabolism under such conditions to the food nutrient ingested, as though it were a part of a complete diet, tacitly involves certain untenable assumptions. At submaintenance levels of food intake, some of the energy represented by the heat produced is derived from body tissue, and, at the fasting level, all of the heat is derived from the oxidation of body substance. With fasting as a base line, a comparison with the heat production of a feeding period tacitly assumes that the dynamic effects of body protein, fat, and carbohydrate are exactly equal to the dynamic effects of these same nutrients when derived from the food at a supermaintenance level of intake. This is fundamentally unsound. It has been shown in a variety of ways, and with several species of animals, that the typical reaction of an organism brought about by a restricted intake of food is an adaptation in the direction of economy of utilization. Thus, with an intake less than its "maintenance requirement," an animal will not only continue to exist (at a diminished level of heat production) but will actually grow, especially if the growth impulse is dominant at the time.

The heat production at a submaintenance plane of nutrition is a difficultly measurable value, without standard significance, since its magnitude decreases with the continuance of the submaintenance status. Furthermore, nutrition at a submaintenance level is irksome to the experimental subject and may, therefore, lead to inconsistent response to the food. Therefore, the heat production of fat and the basal heat production differ in character from that of the higher planes of intake. The imperative necessity for rigid physiological economy dictated by a submaintenance intake is not operative when food is to be had in abundance.

In addition to the point concerning the origins of the nutrients, there is also the question of the quantitative relationships between food nutrients oxidized at the two levels to be compared. For instance, suppose that the dynamic effect of carbohydrate is to be studied by comparing the metabolism of the fasting subject with the metabolism following the ingestion of carbohydrate. In the fasting animal, most of the heat will be derived from fat, with perhaps only two–five per cent from carbohydrate. In the period following the ingestion of carbohydrate, very little if any fat will be oxidized, most of the heat being produced from carbohydrate. It is obvious that the difference in total heat productions between the two periods obtained by subtraction is of questionable significance. Under normal circumstances, neither protein, nor carbohydrate, nor fat is consumed as an entity, but as a part of the diet. Even when superimposed on a complete diet consumed at the maintenance level, an individual nutrient is not utilized as a single unit, but along with the diet as a whole, of which it becomes a part. Thus, the addition of a single nutrient to a complete diet changes the proportion of all nutrients in the diet. The amount of food eaten is ordinarily more important in determining its dynamic effect than is its composition.

In a study of the dynamic effects of food components superimposed on a complete basal maintenance diet, Forbes and Swift[5] found that mixtures of carbohydrate and protein, carbohydrate and fat, and protein and fat resulted in 12, 35, and 54 per cent less dynamic effect, respectively, than the additive individual values. "The dynamic effects of mixed supplements of protein and fat, and of carbohydrate and fat, were lower even than the dynamic effect of fat. In this sense, fat is much more potent than are protein and carbohydrate in determining the dynamic effects of diets."

"In the separate determinations of the dynamic effects of supplementary beef protein, cerelose, and lard it was observed that the dynamic effect of the protein was 32 per cent, of the carbohydrate 20 per cent, and of the fat 16 per cent of their respective gross energy or fuel values; and such individual values are generally but erroneously considered to apply to normal diets in which these nutrients occur variously combined. Upon such individual values, commonly determined at planes of nutrition below energy equilibrium, depends the prevalent misconception that the dynamic effects of diets differ in accord with their protein contents." For scientifically sound interpretation of the dynamic effect of food nutrients, the entire increase in metabolism, rather than the maximum height to which it rises, must be measured, and the plane of intake in both periods compared must be at, or above that of energy equilibrium.

Under experimental conditions which satisfied these requirements, it has been firmly established from extensive work with albino rats at the Department of Animal Nutrition of the Pennsylvania State College that the efficiency of energy utilization of diets, furnishing equal quantities of protein and energy, increases with increasing dietary fat content.[1, 2, 6, 7, 8, 9, 10] It is this series of studies which I would like to present. In view of the foregoing discussion, it will be necessary to describe in some detail the experimental conditions which were imposed to safeguard the validity of conclusions. In the first series of experiments, four diets were formulated containing approximately 2, 5, 10 and 30 per cent fat, respectively. All diets contained two per cent corn oil, additional fat being supplied in the form of lard. Every precaution was taken to insure adequate amounts of minerals and vitamins. The diet containing two per cent fat was arbitrarily made to contain 20 per cent protein. By means of an algebraic computation, based on the nitrogen and on the energy contents of the nonnitrogenous nutrients, the other three diets were compounded to make the ratio of the energy of the protein to the energy of the diet as a whole, constant in all four diets. Then, by the use of so-called isocaloric factors, it was possible to compound and to feed the 4 diets so as to supply identical amounts of protein and energy. For instance, 7.03 grams of the diet highest in fat (30 per cent) contained exactly the same amount of protein and energy as did 10.00 grams of the diet lowest in fat (2.00 per cent). The difference between the diets as fed concerned the source of the nonprotein energy. The low-fat diet and the high-fat diet could as logically be referred to as the high-carbohydrate diet and the low-carbohydrate diet, respectively. The gross energy values of all dietary components were determined with the bomb calorimeter. Verification of the computed energy content of each diet was accomplished by the same means.

The first of these experiments was conducted with 10 groups of 4 male weanling quadruplets, each rat of each quadruplet, from a given litter, being fed the diet containing 2, 5, 10, or 30 per cent fat, respectively (see TABLE 1). The composition of the bodies at the start of the experiment was computed from the analysis of the bodies of litter mates sacrificed at that time. The feed intake was adjusted daily as determined by the individual in each group of four which ate the least. Feces and urine were collected quantitatively each day. At the end of the 70-day experimental period, the rats were killed, and the nitrogen and energy content of the bodies was determined. A single measurement of the heat production for each rat was obtained by subtracting from the energy of the feed, the energy of the excreta, and body gain.

This method of indirect calorimetry is exceedingly accurate. It is limited to small animals and to one observation over a long period of time. The composition of the bodies of weanling rats from the stock colony has been found to be very uniform so that the composition of the experimental rats at the start of the experiment may be computed with confidence. This uniformity in body composition is not found in mature rats, so that, for maximum accuracy, this method of indirect calorimetry is further limited to the use of young uniform animals at the beginning of the test period. The results of this first experiment[6] showed that the heat production of the rats decreased, and that the energy retained by the rats increased in a regular manner with increasing dietary fat.

As compared to the diet containing two per cent of fat, there was 13 per cent more energy retained by the rats receiving the diet containing 30 per cent of fat. The increase was most marked between the two diets containing two and five per cent of fat, respectively. About 75 per cent of food energy is disposed of as heat, which may be considered as the chief end-product of food.

A second and similar 70-day metabolism and body-analysis experiment[8] was conducted, except that only three levels of fat were included, namely 2, 10, and 30 per cent. Twelve rats were used for each diet, each rat having a litter mate on each of the other two diets. There was again a definite and regular decrease in heat production and an increase in energy retention with increasing dietary fat.

A third experiment[10] with growing rats was conducted in a manner similar to the first two, but in which only two levels of fat (2 and 30 per cent) were involved, and in which the protein level was made sub-optimum (7 per cent). Again, using 12 litter-mate, male, weanling, albino rats on each diet, and supplying identical amounts of protein and energy to each rat of a pair, it was found that increased body gains of fat and energy and decreased heat

TABLE 1

PARTITION OF AVERAGE DAILY INTAKE OF FOOD ENERGY PER RAT DURING 70 DAYS

Fat content of diet, per cent	*Energy Intake, Cal.*					*Energy Output, Cal.*			*Energy retained, Cal.*
	Gross energy intake	*Protein*	*Carbo-hydrate*	*Fat*	*Metabo-lizable*	*Feces*	*Urine*	*As Heat*	
2	2854	799	1912	143	2601	128	125	2195	406
5	2854	799	1713	342	2605	126	123	2165	440
10	2854	799	1456	599	2610	121	123	2154	456
30	2854	799	657	1398	2615	123	116	2155	460

TABLE 2

PARTITION OF DAILY FOOD ENERGY AND DYNAMIC EFFECTS

Plane of nutrition	*Diet No.*	*Intake*		*Feces, Cal.*	*Urine, Cal.*	*Metabolizable energy, Cal.*	*Heat production, Cal.*	*Gain, Cal.*	*Dynamic effects Cal.*
		Nitrogen, mg.	*Energy Cal.*						
Maintenance	1	352	44.64	2.25	2.75	39.64	30.50	9.14	—
	2	352	44.64	2.35	2.75	39.54	29.93	9.61	—
	3	352	44.64	2.16	2.75	39.73	29.50	10.23	—
	4	352	44.64	2.53	2.76	39.35	27.56	11.79	—
Super Maintenance	1	512	64.93	3.30	3.91	57.72	37.79	19.93	7.29
	2	512	64.93	3.27	3.92	57.74	36.32	21.42	6.39
	3	512	64.93	3.20	3.93	57.80	35.28	22.52	5.78
	4	512	64.93	3.58	3.96	57.39	31.66	25.73	4.10

production were associated with the high-fat diet. The level of dietary protein is apparently not a factor in the superior energy utilization of high-fat diets exhibited by growing albino rats under conditions of normal cage activity. Statistical studies of the data in all experiments established the high validity of conclusions.

All the data referred to up to this point were obtained from experiments with young growing animals during a period of 70 days under conditions of normal cage activity. The diets used in the first two experiments cited above were also used in comparable studies with mature rats with activity excluded.[7, 9] These studies with mature animals were conducted by the open-circuit, respiratory-quotient method of Haldane. Voluntary activity was excluded by subjecting the rats to a bright light. Forty-eight male mature rats from 12 litters (four from a litter) were used in the first experiment, with 12 rats on each diet. The rats were fed maintenance quantities of the four experimental diets for ten days, given in equal portions twice daily, to adapt them to this plane of metabolism and to establish them, as far as possible, on a uniform rate of metabolism throughout the day. It was intended that this amount of food should maintain the animals in positive energy balance.

This ten-day preliminary maintenance period was followed by eight-days' feeding on the same quantities of the diets (11.0 grams daily of the diet lowest in fat, isocaloric quantities of the other diets), with collection of the excreta for the determination of nitrogen balance and metabolizable energy. Then followed two days of respiration measurement on these maintenance diets. The subjects were next given the supermaintenance quantities of the same diets for five days to adapt their heat production to this level of food intake, the weight of the diets being 16 grams for diet No. 1, and somewhat less for the diets of higher fat contents as required to provide isocaloric food intake. Next followed two days of respiration measurement, and finally an eight-day period of excreta collection, on both the supermaintenance diets.

A purpose in the order of feeding treatment, as recounted, was to have the respiration experiments on the two planes of food intake as close together as possible, that is, separated only by the five days required to establish the animals in heat production representative of the higher plane of food consumption.

During the two-days' measurements of the heat production, the rat, after receiving food at 6:30 A.M., was put into the respiration apparatus at 8:00 A.M., where it remained until 3:00 P.M. Of course, this seven-hour period did not completely satisfy the requirement that the entire heat increment be measured. It was fully realized that the height and duration of dynamic effect might vary with the character of the diet. However, by giving equal amounts of food twice daily to minimize this possibility, the entire procedure seemed the best that could be devised in deriving heat increments representing the metabolism in the absence of voluntary activity.

Heat production computed from the oxygen absorption and carbon dioxide production again decreased consistently with increasing fat content of the diet. Body gain of energy increased similarly as the fat content of the diet covered the range 2, 5, 10, and 30 per cent.

Since the four diets supplied approximately equal quantities of metabolizable energy, the body gains of energy are in reciprocal relation to the heat productions and, being of lesser magnitude, exhibit a much greater percentage change with increasing fat content of the diet. At the "maintenance" level, which was safely above that of energy equilibrium, the body gain of energy in case of the diet lowest in fat was 39.64—30.50 = 9.14 cal. At the same level of intake of protein and energy, but with a 30 per cent fat content, diet No. 4 produced a body gain of 39.35—27.56 = 11.79 cal.—an increase in body gain of 29 per cent as compared to diet No. 1. A similar comparison at the supermaintenance levels reveals an increase in body gain of energy of 29.1 per cent (see TABLE 2).

In addition to these convincing comparisons, we may also compare the heat increments of the low- and high-fat diets. The heat increment, or dynamic effect, of the low-fat diet, as determined between two planes of intake (both above that of energy equilibrium), was 37.79—30.50 = 7.29 cal. The corresponding value for the high-fat diet consumed at the same two levels of intake of protein and energy was 31.66—27.56 = 4.10 cal. Body gain of energy for the low-fat diet was increased 10.79 cal. (19.93—9.14) in going from the maintenance to the supermaintenance plane of intake. The corresponding value for the high-fat diet is 13.94 cal. Thus, the body gain of energy resulting from an increase in intake of a diet high in fat is 29.2 per cent greater than that resulting from identical intakes of protein and energy contained in a diet low in fat.

This entire series of observations was repeated the following year with mature rats, using the same diets as were used in the second 70-day experiment with young growing rats.[9] Three diets containing 2, 10 and 30 per cent fat, respectively, were fed to 12 groups of litter-triplicates. The findings again demonstrated that the fat component of the diet resulted in economy of utilization of food energy. These heat increments or dynamic effects, determined with mature rats with activity excluded, were measured as the difference in heat productions from maintenance and supermaintenance quantities of diets containing from 2 to 30 per cent of fat, so compounded and fed as to supply equal quantities of gross energy, protein, and vitamins.

Using diets similar to those in this whole series of observations, a final study was made[2] in which the total metabolism of mature rats was measured continuously throughout a period of 48 hours, with subdivision into consecutive 3-hour periods. During this time, the rats were fed and allowed freedom to move about in the cage. The specific purpose of this experiment was to determine the changes in metabolic activity in the rat during a 24-hour cycle when diets with either a low (2 per cent) or a high (30 per cent) fat content were fed. The procedure used for the measurement of the heat production, known as the carbon and nitrogen balance method, depends on (a) a measured and constant food intake, (b) the collection and analysis (carbon, nitrogen, and energy) of the urine and feces, and (c) the measurement of the carbon dioxide eliminated by the lungs. From the gain of nitrogen are computed the equivalent quantities of protein, carbon, and energy gained.

From the intake of carbon are subtracted the quantities of carbon eliminated in the urine, feces, and carbon dioxide, as well as the carbon content of the protein gained, the remainder being the carbon gained as fat. Finally, the heat production is computed by subtracting from the energy intake the energy of the feces, urine, and body gain.

The special advantage of the carbon and nitrogen balance method is that it permits the measurement of the total effect of a diet, for protracted periods, on the metabolism of an animal, including values for protein and fat gained or lost as well as the heat production, under normal conditions as to physical activity. This method of indirect calorimetry has been used extensively with large animals during a period of many years and has given results exceedingly concordant with those simultaneously obtained by direct calorimetry.

The subjects in this last test were 24 mature male rats, with 12 rats in each of two groups. The daily feed was divided into two equal parts, which were fed exactly 12 hours apart at 8 A.M. and 8 P.M. The apparatus used in this study[4] consisted of individual, water-sealed, cylindrical chambers made of sheet copper, inside which the rat was confined in a cage constructed of ⅓-inch-mesh galvanized-iron screen. Feed intake was constant for a period of 20 days prior to the respiration measurements. During the last ten days of this period, feces and urine were collected quantitatively, while in the respiration chambers feeding was continued as usual. This was accomplished by stopping the ventilation for a moment and introducing the feed through a copper funnel soldered into the top of the copper cage directly above the feed beaker.

In order to determine the changes in metabolism throughout the 48 hours, the ventilation of the chamber was stopped long enough every three hours to weigh the absorption tubes. This required only about three–four minutes on the average and was of such short duration that it did not permit any appreciable increase in carbon dioxide concentration in the respiration chamber. Any accumulation of carbon dioxide was thoroughly removed during the ensuing 3-hour period. On a 24-hour basis, the high-fat diet again produced less heat than an equicaloric diet of low fat content, the odds of significance being 205 to 1. The tendency of a high-fat diet to produce less heat than an equicaloric diet of low fat content is not as pronounced when the experimental conditions involve mature rats with unrestricted activity (as in the case just described) as it is when activity is restricted or when young animals are used (see FIGURE 1).

It is of interest to note that dynamic effects following the evening meal are higher with both diets than that following the morning meal. The rats were noticeably more active in the evening. The increase in heat production during the morning seems to be largely a true dynamic effect, since it did not start until food was given. It is also worth noting that, at certain times of day (just before feeding), the heat production of the rats receiving the high-fat diet was greater than that of their pair mates receiving the low-fat diet. At 4 A.M., the metabolic activity was greater than at any time following the morning meal.

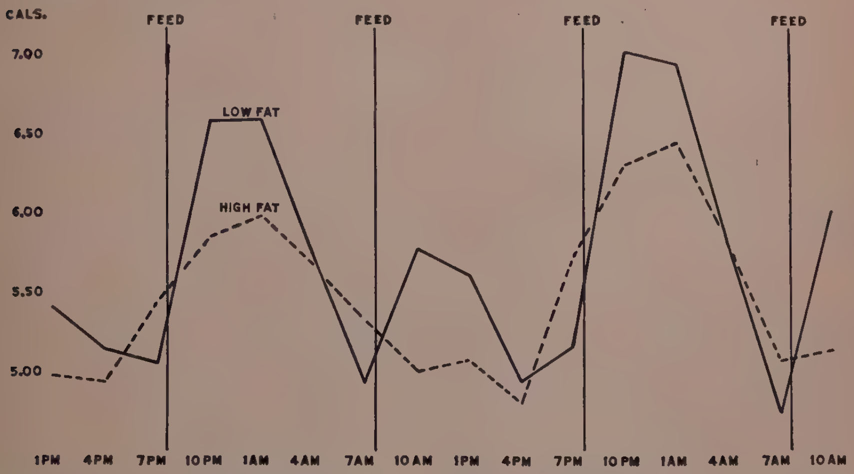

FIGURE 1. Curves of heat production per 3-hour period of rats on diets of high and low fat content.

A recent report from Michigan State College[3] deals with the relative effectiveness of high- and low-fat diets in bringing about weight loss in overweight college students. Energy intakes and energy outputs were not precisely measured, and the data from one subject were discarded as they indicated that the subject did not adhere to the diet. From their other data, the authors felt justified in concluding that a diet high in fat is the more effective as a reducing diet. "The subjects reported a feeling of well-being and satisfaction. Hunger between meals was not a problem." In the formulation of reducing diets it would appear that the satiety and "staying-power" qualities of dietary fat may more than offset its high energy content. A diet rather high in fat may be more acceptable to the subject existing at a submaintenance level of intake than an equicaloric diet high in carbohydrate. As shown in FIGURE 1, there is a more uniform metabolism throughout the 24-hour day when the diet is high in fat. In any case, the total energy intake must be less than the energy output to produce loss of body fat.

To digress from the subject of dietary fat to dietary protein for a moment, extensive work from our laboratories, concerning the dynamic effect of equal-energy-content diets containing from 5 to 45 per cent of protein, shows conclusively that less heat is produced with increasing protein content of the diet. The difference in total heat production was in the order of three per cent. This has been reported in a series of 6 papers covering a period of years. Diets high in protein have a lower dynamic effect and are more efficiently utilized than are equicaloric diets of a lower protein content. This fact is not yet widely recognized chiefly due to the high dynamic effect of protein when fed as a single nutrient to a fasting animal, this finding having been given considerable emphasis many years ago by Rubner and others.

In a comparison of high- and low-protein diets, Pitts and associates,[13] working with human subjects, report an insignificant difference in metabolism (reclining or standing) and in the performance of work in a hot environment. Glickman and associates[11], also working with humans, have pointed out that the dynamic effect of food is a minor item in the metabolism of active men and that high-protein or low-protein meals exert an inappreciable effect on heat production. This was found to be the case when the environmental temperature was either high or low. Their observations covered periods of observation of from six to seven hours, postprandial.

Although the theory, advanced by Liebig, that protein was the sole source of energy available for muscular activity, while fat and carbohydrate furnished only heat, was proved utterly untenable by Voit in 1866, the belief that Liebig was correct persisted in many minds for a long time afterward. Similarly, the incorrect understanding that diets high in protein produce more total heat than equicaloric diets of low protein content will disappear only gradually.

In addition to these studies of energy utilization which I have briefly reviewed, we have been interested in the comparison of high-fat and low-fat diets with regard to long-time effects. At our laboratories, we are at the point of finishing some studies of this nature with rats which have involved diets of low and of high fat content fed continuously for a long period. Observations have included effects on longevity, reproduction, and lactation.

Three diets were fed *ad libitum*. The control diet consisted of a commercial-laboratory rat diet that had given satisfactory reproduction and lactation for several years in the breeding colony. The other two diets, one high in carbohydrate and one high in fat, were prepared by incorporation of 20 per cent of sucrose or 20 per cent of corn oil, respectively, into the colony diet. Both of these two experimental diets were supplemented with liver powder, yeast, and vitamins to offset the dilution of known and unknown factors brought about by the addition of the sucrose and corn oil.

With an average number of 78 matings for each diet, a significant decrease in reproduction performance of rats receiving the 23 per cent fat diet was observed when compared to the control (4.4 per cent fat) or to the high carbohydrate (3.4 per cent fat) diet. This was manifest in smaller numbers of lighter-weight young in litters of the high-fat group.

Lactation performance, measured on an average number of 350 young for each diet, revealed no impairment due to the high-fat diet when compared to the control diet. However, a significant improvement in lactation resulted from the high-carbohydrate diet. Male and female fertility were excellent in all diet groups, and continued through all generations.

In summary, any studies of the dynamic effect of food must provide that the planes of nutrition involved be at or above that of energy equilibrium. The dynamic effect of a single nutrient, determined directly, bears no significant relation to the dynamic effect of diets of which the nutrient becomes a part. The dynamic effect of a complete diet is less than the sum of the dynamic effects of its components as determined individually. In extensive work with young and with mature albino rats at planes of intake above the point of energy equilibrium, it has been clearly demonstrated that dietary fat confers economy of utilization upon the energy of the entire diet. Identical quantities of protein and energy were involved in all cases, the only difference in the diets compared being in the source of the nonprotein energy.

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FAT ABSORPTION AND THE EXPERIMENTAL BASIS OF ORAL FAT EMULSIONS

By Robert P. Geyer

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The important physiological sites usually considered in the absorption of fat from the intestine are the intestinal lumen, the intestinal wall, and either the portal blood or the intestinal lymph. On the basis of present knowledge, it seems reasonable to assume that the reactions occurring in these locations are not completely independent, but interdependent, in that the products of the reaction in one place become the reactants in the next. The mechanisms involved in the reactions themselves, and the mechanisms whereby the products of each reaction are passed on to the next locale have been the subject of much investigation, but they are not entirely understood or above controversy. The present paper is not intended as a critical review of the various theories that have been advanced, but rather to discuss those phases of the problem which have a bearing on the design and use of oral fat emulsions.

The two main theories of intestinal fat absorption are those of Verzar and McDougall,[1] and of Frazer and co-workers.[2] They differ mainly in the degree to which lipolysis is assumed to occur in the intestinal lumen, and in the fate of the products of this lipolysis. The former theory assumes complete hydrolysis of the triglycerides, followed by the direct absorption of the fatty acids produced. Frazer's theory, commonly called the "partition theory," assumes the following steps: (a) partial hydrolysis of the triglycerides to yield mono- and diglycerides, free fatty acids, and glycerol; (b) simultaneous emulsification of the rest of the triglyceride by means of the system comprised of fatty acids, monoglycerides, and bile salts; and (c) absorption of the emulsified triglycerides by way of the lacteals, lymphatics, and thoracic duct, while the free fatty acids are absorbed directly into the portal blood. The two theories are least divergent when triglycerides of short-chain fatty acids are considered. Such fats probably undergo emulsification and essentially com-

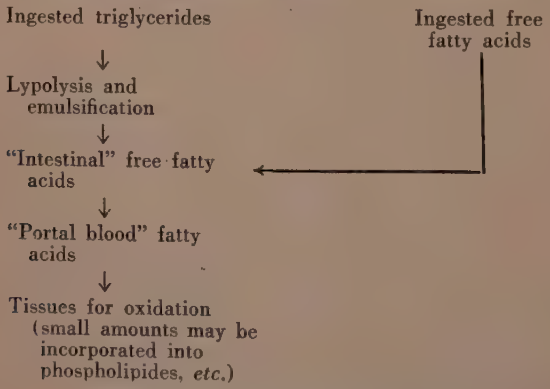
Ingested triglycerides
Ingested free fatty acids
Lypolysis and emulsification
"Intestinal" free fatty acids
"Portal blood" fatty acids
Tissues for oxidation (small amounts may be incorporated into phospholipides, *etc.*)

FIGURE 1. Fate of short-chain fatty acids and triglycerides.

plete lipolysis in the intestine to yield free fatty acids and glycerol. As shown in the simplified scheme presented in FIGURE 1, the free acids are then absorbed as such, and transported in the blood stream to the various tissues for oxidation or perhaps limited incorporation into tissue lipids.

When the triglycerides are comprised of long-chain fatty acids, however, the situation is much different (see FIGURE 2). Complete hydrolysis as required by Verzar's theory would, of course, result in nothing but fatty acids and glycerol, and the fatty acids would presumably be absorbed as such, as shown by the descending series of reactions on the right hand side of the diagram. In contrast, Frazer's theory states that only a portion of the fat undergoes these reactions, while the rest of it follows the sequence of reactions on the left hand side of the diagram. The experimental data upon which these theories were founded can be found in the original publications cited in the bibliography and in subsequent papers and will not be restated here. Instead, reference will be made to more recent experiments in which the radiotracer technique has been employed.

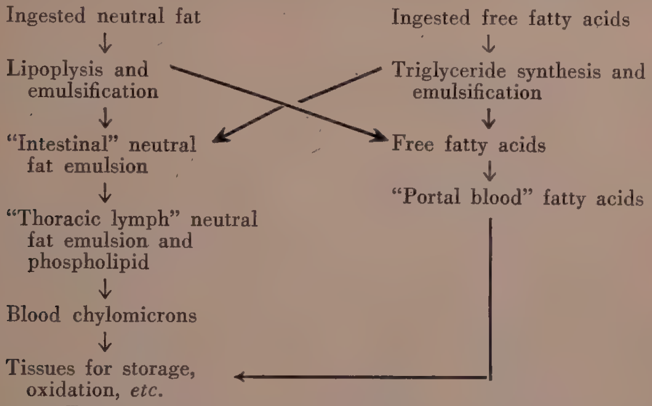
Ingested neutral fat
Lipoplysis and emulsification
"Intestinal" neutral fat emulsion
"Thoracic lymph" neutral fat emulsion and phospholipid
Blood chylomicrons
Tissues for storage, oxidation, *etc.*
Ingested free fatty acids
Triglyceride synthesis and emulsification
Free fatty acids
"Portal blood" fatty acids

FIGURE 2. Fate of long-chain fatty acids and triglycerides.

The studies in which fatty acids and their triglycerides have been labelled with carbon fourteen and used to study fat absorption have a distinct advantage over older investigations in that a neat and definite marker allows the original substrates to be followed easily and accurately. As might be expected, however, it is easier to ascertain where the radiocarbon is than to determine how it arrived there. The relative complexity of reactions involving mixed triglycerides and the products derived from them cannot be minimized.

Most of the experiments with radiolipides have been conducted as follows: The labelled fatty acid or its triglyceride was mixed with a liquid oil, and fed by stomach tube to rats which had been cannulated either in the intestinal or thoracic lymphatics. The lymph was collected for 24–48 hours and assayed for radioactivity in the various lipide fractions. The respired $C^{14}O_2$ was generally not determined. TABLE 1 shows the results reported by various investigators and includes the studies of Reiser and Bryson[5] in which nonradioactive isomerized linoleic acid was used. (The values given are

TABLE 1

RECOVERY OF ORALLY ADMINISTERED FATS AND FATTY ACIDS IN THE THORACIC DUCT LYMPH

Substrate	*Per cent recovered in lymph in 24 hr.*	*Per cent of lymph radioactivity recovered in phospholipide*	*Reference*	*Investigators*
1 C^{14}-Palmitic acid or 1 C^{14}-Tripalmitin	81-87	10	3	Borgstrom
1 C^{14}-Palmitic acid or 1 C^{14}-Tripalmitin	70-92	4	4	Bloom, *et al.*
Conjugated linoleic acid or its triglyceride	40	—	5	Reiser and Bryson

approximate. The reader is referred to the original papers for the actual values.) It is obvious that, under the conditions of these experiments, no difference was found in the ultimate fate of the radiocarbon, whether it was given as a fatty acid or a triglyceride. The various authors cite their results as being evidence against the Frazer theory of fat absorption.

The radiocarbon experiments show that both reactions of synthesis and of degradations are probably involved in fat absorption. It is important to know whether the free acids were converted to neutral fat in the intestinal lumen or in the intestinal wall. Should the former site be the case, it could be argued that much of the original free fatty acid was incorporated into neutral fat before absorption took place. Also needed are experiments in which the radiolipides are fed to cannulated rats in a mixed diet in order to approximate the normal dietary state. Although a large dose of oral fat emulsion in the human may be likened to the stomach tubing of the oils in the case of the rat, most users of the oral emulsions have other food available. As more information on the mechanisms of fat absorption becomes available, it can be applied to the formulation of oral fat emulsions.

Unfortunately, even if the mechanisms of fat absorption were fully understood, the problem of supplying an emulsion of fat completely suitable for routine use would still be difficult because many other factors are also

TABLE 2

SOME REQUIREMENTS OF AN IDEAL FAT EMULSION

Physiological location	*Requirement*
Mouth	Satisfactory taste Pleasant physical characteristics Nonobjectionable aftertaste
Stomach	Stable to low pH Not retained abnormally long Nonnauseating
Intestine	Stable to intestinal contents Readily absorbed No tendency to cause diarrhea

important. It is still impossible to list the exact qualifications of the perfect fat emulsion for oral use, but a list of desirable characteristics is shown in TABLE 2. Fortunately, emulsification itself greatly reduces the unpalatability associated with the ingestion of large quantities of oil, and also helps to decrease the aftertaste. Flavorings, of course, offer another means of disguising the taste of oils.

The most difficult obstacle confronting oral fat emulsions is the low pH of the stomach, which invariably causes much of the emulsified fat to coalesce and form large globules of oil. To what extent the degree of dispersion of the oil influences gastric retention is not known, but the evidence available indicates such an influence may exist. This would be important to avoid a feeling of fullness which some persons experience after the ingestion of a large amount of fat. The relationship of the degree of dispersion of the oil to undesirable side effects such as nausea, vomiting, and diarrhea is not known at present.

Little success has been achieved in obtaining stability to gastric conditions using emulsifiers of practical importance. Rather than recite a long list of negative results, a few of the most interesting ones are given in TABLES 3 and 4. The studies from which these data are taken[6] were designed to evaluate the role of emulsification in the absorption of fat and also to determine factors affecting stability of emulsions of oil in the stomach and in the

TABLE 3

ABSORPTION OF CORN OIL* GIVEN ORALLY TO RATS

Preparation	*Mean per cent absorbed*	
	In 2 hr.	*In 4 hr.*
Corn oil–phosphatide emulsion	38± 9†	79± 8
Corn oil–gelatine emulsion	41± 9	72±11
Unemulsified corn oil	36±10	70±10

* Approximately 350 milligrams corn oil given per rat.

† Standard deviation of the mean.

TABLE 4

ABSORPTION OF OILS* BY RATS FOUR HOURS AFTER INTESTINAL INSTILLATION

Preparation	*Mean per cent absorbed*	*Difference*
Corn oil–gelatine emulsion	44 ± 9†	26
Corn oil–gelatine mixture	18 ± 9	
Corn oil	16 ± 5	—
Mineral oil–gelatine emulsion	25 ± 9	23
Mineral oil–gelatine mixture	2 ± 2	

* Approximately 250 milligrams oil given per rat.

† Standard deviation of the mean.

intestinal tract. The lipid preparations used to obtain the data in TABLES 3 and 4 were as follows: an emulsion of corn oil or mineral oil stabilized with soybean phosphatides, unemulsified mixtures of corn or mineral oil with gelatine or phosphatides, and the unemulsified oils alone. The data in TABLE 3 show that emulsification had no effect on the absorption of these oils when they were administered orally. This was probably caused by the instability of these emulsions in the presence of gastric contents. When these same preparations were instilled into isolated intestinal loops, only the gelatine-stabilized emulsions were stable to the intestinal contents. Therefore, only the results with these preparations are given in TABLE 4. As can be seen, emulsification caused a very significant increase in the absorption of both the vegetable and mineral oils. This would indicate that finely divided fat particles can be absorbed from the intestine, and emphasizes the desirability of having fat emulsions for oral use stable to intestinal conditions, especially where the normal emulsification potential is limited.

The problem of devising an ideal oral fat emulsion is still being actively pursued. TABLE 5 shows the composition of an emulsion that has been used extensively in humans and in animal studies. It is largely unstable to the normal gastric and intestinal contents, but furnishes a large number of calories in a small volume, is reasonably palatable, and is tolerated fairly well. As new information and new stabilizers become available, it appears probable that progress will continue toward the goal of establishing the ideal oral fat emulsion.

TABLE 5

COMPOSITION OF ORAL FAT EMULSION

Ingredient	*Weight per cent*	*Calories per 100 milliliters*
Fat	40	360
Dextrose	10	40
Stabilizers	2.2	15
Preservatives	0.1	—
Antioxidants	0.05	—
Flavors	—	—
	Total	415

In considering fat emulsions for oral nutritional purposes, compounds which might promote the absorption of fat from the intestine cannot be overlooked. Our own attempts to demonstrate any increased absorption of fat following the administration of compounds such as phosphatides, choline, and Tweens have given negative results.[7] On the other hand, these compounds have been reported to give positive results by various investigators.[8, 9, 10] Further studies are necessary to clarify this problem, and much work remains to be done in situations where normal emulsification and absorption are impaired.

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CLINICAL STUDIES ON THE USE OF AN ORAL FAT EMULSION*

By Milton Shoshkes†

Clinicians have long known the need for caloric supplementation in therapeutics. Anorexia is a common symptom of illness, leading to negative nitrogen balance and weight loss. The secondary consequences of chronic undernutrition manifest themselves frequently in complaints of excessive fatigue, weakness, restlessness, irritability, insomnia, and, most important, further anorexia. If the presenting illness produces hypermetabolism, as do febrile illnesses and many types of malignancies, these effects are exaggerated and magnified.

Protein and carbohydrate food supplements have been extensively investigated for use in this problem, and have been administered successfully as oral caloric supplement in infants, children, and adults. The major obstacle to their usefulness lies in the excessively large bulk necessary to administer substantial calories. When ingested in large quantities, their tendency to fermentation in the gastro-intestinal tract can result in troublesome diarrhea. Although fat contains 2½ times as many calories per gram as carbohydrate or protein, it was previously impossible to consume it in quantities sufficient to add significantly to the caloric intake.

The emulsification of fat in water makes possible the preparation of a liquid fat in a form which is potable and palatable. A stable emulsion, with a fine particulate fat dispersion, has the characteristics of its watery external phase, and can therefore be mixed with watery solutions or dissolve water-soluble compounds.

Previous work in our laboratory[1, 2] demonstrated that, in rats, orally fed emulsions were no better absorbed than their unemulsified components, and the intact animal could not increase its rate of fat absorption with the addition of exogenous emulsifiers. This was demonstrated to reflect the breakdown of the emulsions within the gastro-intestinal tract. Within an intestinal loop, a stable emulsion with particles less than three microns in diameter was demonstrated to be more easily absorbed than its unemulsified components, but it has not yet been possible to prepare an emulsion that would remain stable when exposed to both gastric and intestinal juices.

The emulsion used in this investigation consisted of 40 per cent peanut oil, ten per cent sucrose or dextrose in water, and 2 per cent purified soybean phosphatide and 0.2 per cent synthetic emulsifier (alkylarylpolyether alcohol) as stabilizers, with small amounts of a flavoring agent, and antioxidant and preservative. The average size of the fat particles was 0.5–1.0 micron, and the dispersion remained stable at room temperature for 6 months. The caloric value was four calories per milliliter. The emulsion contained 7.3 milliequivalents of sodium per liter (172 mg./l.) and 8.0 milliequivalents of potassium per liter (312 mg./l.). It flowed freely even at temperatures of

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* The above work was performed during the tenure of a Fellowship in Nutrition in the School of Public Health at Harvard University, Boston, Mass.

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5°C., was easily administered by glass or tube feeding, and passed easily through rubber nipples. Its taste could be modified by a variety of flavoring agents and still remain stable for a reasonable period of time.* Another emulsion consisting of 50 per cent peanut oil with the same other constituents was also studied in a small number of cases, but was discarded because of inability to flow freely after chilling.

Studies were first obtained in a group of healthy young adult subjects who were below their ideal weights despite determined efforts to gain. Initial empirical doses of 125–250 ml. were administered as an evening drink spaced between the last meal and bedtime. The time of ingestion of the emulsion was chosen as that least likely to impair the appetite for a scheduled meal and most probably be digested completely in the night period. Of the 33 healthy adults, 25 tolerated this large amount of extra fat, and gained between one and 11.5 pounds of weight over periods of study ranging from five to 53 days. Further calculation revealed that the average daily gain in weight was equal to the weight of the extra fat that had been ingested. This, of course, was based upon the average fat consumption of the entire group that continued on the study and should not be transferred exactly to the response of each individual subject. The fat emulsion was also administered to 108 ill adults hospitalized for a wide variety of acute and chronic illnesses that encompassed a large experience of medical and surgical conditions. The only criterion used for their inclusion in the group was a manifest need for extra calories. In ten of these patients, the observations were too incomplete to include in this report except to state that they tolerated the emulsion well. Of the remaining 98, 73 tolerated the emulsion well in doses of 60–250 ml. per day. Of these, 52 demonstrated a favorable caloric balance as manifested by a weight gain of at least one pound in a minimum period of 5 days administration. Although it is, of course, impossible to dissociate the gain in weight resulting from recovery from illness from that which resulted from the absorption of extra calories, the fact that the weight of these patients was static or falling before the emulsion was administered indicates that much of the result must be attributed to the caloric supplementation to their diet.

The emulsion was usually administered by mouth in the evening nourishment period. It was also used successfully in seven patients requiring tube feedings. Five of these were fed by stomach tube, one by gastrostomy, and one by jejunostomy. In these instances it was best tolerated by mixing it with the previously used tube feeding mixture of combined protein, carbohydrate, and some fat, and administered in the usual manner. With the addition of the fat, the original volume of the feeding could be greatly reduced and, in some instances, a greater amount of calories could be tolerated without gastro-intestinal disturbance than had been possible before. Observed weight gains ranged from one to 22 pounds in study periods of five to 150 days. Calculations of the average daily weight gain revealed that these patients gained twice the weight that could be accounted for by the ingestion

* This emulsion was prepared by the Upjohn Company, Kalamazoo, Mich., and is now marketed as Lipomul Oral.

of the fat. Stated differently, an average of 0.2 lb. of weight per day was gained by the subjects who had ingested an average of 0.1 lb. of fat per day. Rapid weight gains were seen frequently in the first two weeks of administration in many of the markedly malnourished patients. This was then followed by a steady plateau of weight gain, comparable to that seen with the healthy adults.

Twenty-one of the original group of 98 patients failed to gain weight or actually lost weight during the study period: three of these refusing more than one-half of all food offered them, and 14 of the remainder being in the terminal stages of their diseases.

The largest amount of emulsion tolerated in one day by any one patient was 1250 ml. of the 40 per cent fat emulsion containing 500 grams fat ingested in divided doses. The only sign of intolerance was a very mild diarrhea of one day's duration. His previously obtained blood carbon dioxide content of 21.6 milliequivalents/liter fell transiently to 14.5 millequivalents/liter the day afterward.

The emulsion, in doses sufficient to offer substantial caloric supplementation, was well tolerated by 75 per cent of all the subjects studied. A definite weight gain was produced in all of the healthy and in 80 per cent of all the ill subjects who consumed an adequate number of calories via the emulsion. It was further observed that the longer each subject took the emulsion, the more weight was gained, although a few of the subjects, after an initial weight gain, leveled off without further weight changes, despite continued consumption of adequate amounts of emulsion. Although no change of dietary or excretory habits was reported, the only conclusions possible was a reduction in food consumption or an increased fecal fat excretion.

Of additional interest were unsolicited comments from the healthy and hospitalized subjects, which included a marked increase in appetite reported by 19 per cent and an increased feeling of strength and well being in approximately half that number. No satiety or significant appetite impairment was observed with the evening administration of the supplement. The satiety effect of diurnal doses was not investigated.

Symptoms of gastro-intestinal intolerance to the emulsions were soon encountered with the large original doses. In mild cases, an unpleasant epigastric heaviness or discomfort, often with excessive belching, and comparable to that experienced after overeating, was described. More severe symptoms were nausea, vomiting, abdominal cramps, and diarrhea. These severe symptoms were seen essentially only in those to whom the initially large doses of 125–250 ml. were given. The problem of palatability was solved by the addition of chocolate or citrus-juice flavoring to the emulsion. An oily after-taste was another complaint frequently met. This was easily removed by eating a dry cracker after drinking the emulsion.

Although the number of patients accumulated in separate disease entities was small, several clinical observations were striking enough to warrant comment. Five patients with active peptic ulcers noted a marked amelioration of symptoms, as well as a rapid weight gain with the fat supplement. High-fat diets are well established in the therapy of peptic ulcers, and fat emulsions may be expected to exert a similar favorable effect. Uremic patients, despite marked gastro-intestinal irritation, tolerated the emulsion quite well, and, in the instance of one patient treated by artificial kidney blood dialysis, it was felt to have contributed to the favorable outcome. A high-fat, controlled electrolyte diet has received great emphasis in recent years as an adjuvant to the treatment of renal disease associated with azotemia.[3] The emulsion was able to contribute a considerable portion to the caloric requirement of those patients unable to ingest solids because of mechanical or neurological impedance in the mouth or esophagus. The extra calories were of great benefit also in the preoperative preparation of thyrotoxic patients, and should be of similar benefit in the preoperative preparation of other wasting surgical diseases. Observations on the reversal of weight losses in patients with various types of malignancies point to a very useful role in the supportive therapy of the cancer patient.

Its usefulness was limited in chronic pancreatic exocrine deficiency states, as manifested by steatorrhea among other symptoms, unless supplemented with an active oral pancreatic enzyme preparation. This was confirmed in unreported studies on children with chronic cystic fibrosis of the pancreas. It must be assumed that fat emulsions will be of little benefit in most steatorrheas, and should be administered cautiously, if at all.

Patients with subtotal gastrectomies tolerated small doses of the emulsion with difficulty and, in all probability, patients with enterostomies of all types will experience similar difficulties with the emulsion in view of the diminished fat tolerance found in these subjects.

Since fat stimulates the secretion of several enteric hormones,[4] among which are cholecystokinin, effective in gallbladder contraction, and enterogastrone, an inhibitor of gastric secretion and motility, patients with gastro-intestinal obstructive diseases should be given the fat with great caution and biliary tract calculi constitute an absolute contraindication to its use. Similarly, the emulsion should not be taken in too close proximity to a large meal, because of the delay in gastric emptying time induced by the fat.

Approximately 25 per cent of the healthy and hospitalized adults experienced untoward gastro-intestinal symptoms after drinking the emulsion. There was no relationship to sex, size, or age of the subjects, and the most susceptible of these were intolerant to as little as 30 ml. of the 40 per cent fat emulsion, containing 12 grams fat. In most of these there was no evidence of organic disease of the gastro-intestinal tract. Further investigation of the response of the gastro-intestinal tract to concentrated fat may reveal the cause for the unexpected reaction to such small amounts of the emulsion upon these individuals. In any event, a small proportion of the normal population may be expected to exhibit sufficient intolerance to small amounts of concentrated fat as to be unable to obtain an adequate caloric supplementation from this type of food. Since a significant proportion of those intolerant to the emulsions avoided dietary fat scrupulously, it might be assumed that part of the observed intolerance was to fats *per se* rather than entirely to the contents of the fat emulsions.

The controversy over the status of dietary fats in acute and chronic liver diseases has resolved to the point where normal quantities of dietary fat are strongly recommended in the treatment of acute infectious hepatitis and cirrhosis for the optimum therapeutic response.[5, 6, 7] Fat in itself is not hepatotoxic. If fat supplements are indicated in the dietary regimen of such patients to add to their caloric intake, the concurrent ingestion of adequate carbohydrates, proteins and B-complex vitamins in a well-balanced diet, should alleviate apprehension over any potential impairment of liver metabolism.

The relationship of dietary fats to lipemia and cholesterolemia is being intensively studied by many laboratories in efforts to find a link between dietary fats and cholesterol and the etiology of atherosclerosis. Oral fat supplements are designed for use only for short-term therapy, for example, to add to the caloric intake during or after a period of illness, usually for periods of time measured in weeks. In such short intervals, no conceivable effect upon atheroma formation can be expected. Meanwhile, the caloric gain of the emulsion may be of the utmost importance, even to the point of being lifesaving.

The importance of adequate caloric intake was strikingly demonstrated in contrasting the weight gains in the healthy subjects, who were in caloric and nitrogen balance, with the doubled rate of weight gain seen in the hospitalized patients who were in caloric and nitrogen deficit. When presented with the option of depositing the nine calories per gram of extra fat obtained through the emulsion as protein or fat, the healthy subjects accounted for the surplus as body fat, since only 0.1 lb. was gained per day per 0.1 lb. of fat ingested. The hospitalized patients, previously either barely maintaining their weight at suboptimal levels or actively losing weight, gained 0.2 lb. of weight per day from a supplement of 0.1 lb. of fat while on a reasonably constant diet. It may then be inferred that the extra calories were deposited as the second option, as body protein. Thus, two grams of weight as protein can be obtained from the original caloric equivalent in each gram of extra fat if a protein sparing action of the extra fat is assumed. This can occur if the extra fat is burned preferentially to satisfy the absolute caloric need, allowing the ingested protein to participate in the metabolic pool as an amino acid source, rather than be deaminated and burned for calories. Confirmation of this hypothesis was obtained using a diet deficient in proteins as well as in calories. Human volunteers on this diet were able to regain nitrogen equilibrium with the addition of fat emulsion to their diets.[8]

Summary

Emulsions of 40 per cent peanut oil and ten per cent dextrose or sucrose with a caloric value of 4 calories per milliliter were given to 141 human subjects in need of extra calories and proved to be readily accepted as a dietary supplement.

Of 33 unselected ambulant normal adults in need of extra calories, 25

tolerated large amounts of the emulsion easily for periods of study ranging from five to 63 days and gained from 1 to 11.5 lbs. The average rate of weight gain in this group was 0.1 lb. per day for an average ingestion of 0.1 lb. fat per day from the emulsion.

Of 98 unselected patients in need of extra calories, hospitalized for a wide variety of medical and surgical illnesses, 73 easily tolerated large amounts of the emulsion administered by mouth or tube in periods of study ranging from five to 150 days gaining from 1 to 22 lbs. The average rate of gain was 0.2 lb. per day for an average ingestion of 0.1 lb. fat per day.

Of the approximately 25 per cent of the healthy and hospitalized adults who did not tolerate the emulsions well, the common symptoms of intolerance were related to the gastro-intestinal tract. Approximately half of these subjects were also intolerant to dietary fat. This incidence of intolerance to the emulsion is artificially high because the initially empirically chosen doses of the fat emulsions proved to have been excessive. When initial amounts of 60 ml. are used, followed by gradual increments, the incidence of intolerance is much less.

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ORAL FAT EMULSIONS IN THE STUDY OF CALORIE-NITROGEN RELATIONSHIPS IN MAN

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Although the role of fat as an important source of dietary calories is unquestioned, there still is disagreement about its place in the nutritional management of patients. It is usually taken for granted that the goal in feeding patients is primarily to replenish protein stores. However, the extent to which fat in the diet can contribute to this end is controversial.

Some of this controversy has its origin in experiments of the type performed by Kayser on himself and reported by Sherman.[1] This experiment involved the equicaloric substitution of fat for all of the carbohydrate in an otherwise adequate diet, for a period of three days. The subject previously had been in nitrogen equilibrium and when the carbohydrate was replaced entirely by fat he promptly displayed an appreciably negative nitrogen balance.

Citing this and similar experiments, Deuel states[2] that ". . . carbohydrate and not fat has the ability to spare protein in conditions of nitrogen starvation." Recently, Ramasarma in a review of the subject of parenteral nutrition[3] makes reference to Deuel's article in support of the statement that ". . . a nitrogen-sparing action is exerted by carbohydrate and not by fat."

In the nineteenth century, Voit[4] described an experiment on a fasting dog to which he administered 100, 200, and 300 grams of fat per day in successive periods. He observed no change from the fasting level of nitrogen excretion when the fat was given. Accordingly, Voit concluded that the ingested fat merely was oxidized in place of the animal's own body fat.

These experiments require reinterpretation in the light of more recent knowledge about the intermediary metabolism of foodstuffs. In this regard, Peters[5] has reminded us of the relevant distinction which may be made between *operative* metabolism and *energy* metabolism. When it is recognized that carbohydrate and fat have operative as well as energy-producing functions, it can be understood why Rubner's "isodynamic law" cannot be applied to situations involving the total replacement in the diet of one nonprotein foodstuff by a thermodynamically equivalent amount of another.

Actually, as Peters and others have pointed out, glucose participates in operative metabolism in the sense that it provides oxalacetate to the Krebs cycle. If fat is the source of any oxalacetate at all it is an extremely inefficient source. Moreover, carbohydrate is the indispensable fuel of the nervous system.

Thus it may be said that carbohydrate "spares" protein in several ways: First, it relieves it of the responsibility of providing oxalacetate to the Krebs cycle and carbohydrate for the central nervous system. Second, carbohydrate spares protein by relieving it of the job of providing the energy for certain metabolic processes of the body which body fat stores, by themselves, seem unable fully to support.

Dietary fat, by virtue of its caloric properties, also spares protein, but this occurs *after* the requirement for essential quantities of carbohydrate has been met (it has been estimated[6, 7] that about 100 grams of glucose per day will ordinarily cover the need of a normal adult for this essential metabolite).

Moreover, there is evidence that fat itself may have operative functions [8, 9, 10] and for such functions carbohydrate presumably cannot effectively replace dietary fat in metabolism. There probably exists a minimum requirement for the "essential" fatty acids in the dietary of man.[11] Aside from any metabolic properties, fat may favor more efficient utilization of dietary protein by delaying gastric emptying and thereby preventing too rapid absorption of amino acids from the small bowel.[12]

Recently, we reported a series of metabolic studies[13] on volunteer subjects, which involved the use of oral fat emulsions[14] as caloric supplements to calorically inadequate diets. The purpose of these studies was to appraise the influence of calories from fat on protein utilization when the protein intake was marginal. It was believed that such protein intakes would provide a sensitive index to the effect of changing calorie-nitrogen ratios without seriously depleting protein stores. In every instance, enough carbohydrate was supplied daily to cover special requirements for this nutrient.

In TABLE 1 are summarized the findings of metabolic studies on five volunteer subjects with respect to the influence of a changing caloric intake (calories from oral fat) upon protein utilization at constant marginal levels of protein intake. From these data, it may be concluded that (1) the orally administered fat emulsion was well absorbed and was utilized; (2) at marginal levels of protein intake, efficient utilization of the protein takes place only when the caloric intake approximates calculated energy requirements; (3) calories from depot fat are not as available as calories from dietary fat for purposes of nitrogen sparing.

In this paper, metabolic-balance studies involving the administration of oral fat emulsions to a normal volunteer subject and to a patient are presented. The first experiment represents an extension of work previously reported[13] and is an example of an approach we have found to be valuable in the study of calorie-nitrogen relationships. The second experiment is an appraisal of the use of "hyperalimentation" in the management of a patient with defective intestinal absorption.

Procedure and Results

Feces and diet samples, suitably prepared by dilution and homogenization, were analyzed for their content of nitrogen, potassium, sodium, and fat. Urinary potassium, sodium, and nitrogen were measured directly. All determinations were done on aliquot samples.

Total nitrogen was determined by a macro-Kjeldahl method. Total fat was measured by the method of van de Kamer *et al.*[15]

Potassium and sodium were determined by means of a flame photometer,

TABLE 1

SUMMARY OF METABOLIC FINDINGS IN FIVE NORMAL VOLUNTEER SUBJECTS WITH RESPECT TO THE INFLUENCE OF A CHANGING CALORIC INTAKE (SUPPLEMENTARY CALORIES FROM ORAL FAT EMULSION) UPON PROTEIN UTILIZATION AT MARGINAL LEVELS OF PROTEIN INTAKE

Subject	*Weight, kilograms*	*Nitrogen intake, grams/day*	*Average nitrogen balance/day at 1000–1300 calories, grams*	*Calories needed for nitrogen equilibrium*			*Average increase in stool fat during administration of oral fat emulsion, gram*
				Basic diet	*From oral fat emulsion*	*Total*	
H. A.*	66.3	6.7	—3.2	1200	1000	2200	0.95
D. E.*	75.7	6.7	—6.8	1200	2000	3200	0.3
G. C.*	72.8	6.6	—3.1	1300	1800	3100	0.66
H. L.*	51.5	6†	—3.4	1500	1200	2700	—
A. G.	81.6	8	—3.0	1000	1300	2300	—

* Data on these subjects were taken from a previously reported study.[13]

† Intravenously administered.

the fecal and dietary aliquot samples having first been ashed and extracted and made up to volume with dilute hydrochloric acid.

Caloric intake was calculated by means of standard tables[16] from weighed portions and refusals.

Experiment 1. A volunteer subject, A. G. (aged 23), was kept in the

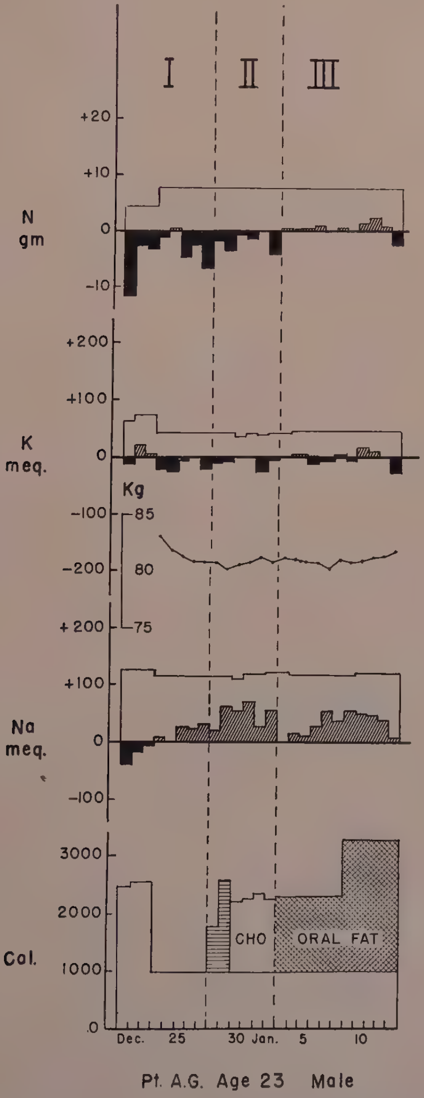

FIGURE 1. Metabolic Chart of Subject. A.G. Effect of supplementary carbohydrate and of oral fat emulsion on the utilization of a marginal amount of dietary protein. The method of charting used in the figures accompanying this paper was developed by one of the authors (F.D.M.). In the case of nitrogen, potassium, and sodium, intake is charted from the zero line up, and output is charted down from the intake line. Accordingly, an excess of output over intake is seen as a black area below the line. If output is less than intake, the difference is represented by crosshatching above the zero line. Further details are given elsewhere.[17]

hospital during the study period. He was not obese and had a history of recent good health. He was allowed up *ad lib.*, and mild exercise was permitted. The experiment may be divided into three general periods, as follows:

Period I lasted eight days. For the first three days, the caloric intake was 2500, and the nitrogen intake was limited to 4 grams per day. For the next five days, the caloric intake was fixed at 1000 calories per day, and the nitrogen intake was raised to 7.8 grams per day. This level of nitrogen intake was kept constant for the remainder of the experiment.

Period II lasted six days. During the first two days, supplementary calories were added to the basic 1000-calorie diet by means of intravenously infused fat emulsions. On the third day, it was observed that the subject had a mild follicular-type dermatitis and the intravenous fat was discontinued. For the following four days, the subject received instead 1300 extra calories per day from orally administered carbohydrate supplements. This was in addition to the basic 1000 calorie diet which was maintained during the entire course of the experiment.

Period III was of eleven days' duration and was divided into two parts: (*a*) For the first six days, the subject was given oral fat emulsion in amounts which added 1300 calories per day to his basic diet. (*b*) For the remaining five days, the intake of oral fat was increased further and provided 2300 extra calories per day.

Results (See FIGURE 1). During the period of low-calorie, low-nitrogen intakes (in Period I), the subject displayed unequivocal nitrogen deficits averaging about 4 grams per day. The potassium deficit averaged about 8 milliequivalents per day. He lost weight rapidly and felt chronically hungry. He also became increasingly irritable.

During Period II, when he was receiving supplementary calories, first from intravenous fat emulsions and then from carbohydrate foods, he felt much more comfortable. However, he continued to have negative nitrogen and potassium balances. The deficits for the six-day period averaged 1.7 grams and 6.8 milliequivalents per day, respectively. He also began to gain weight.

Period III was marked by a return to nitrogen equilibrium. The subject's weight increased slowly and he felt well, even though the high-fat low-protein diet was neither palatable nor satisfying. Indeed, even on an intake of 3200 calories per day he continued to feel chronically hungry. The nitrogen balances for both parts of this period were positive to about the same extent, in spite of the fact that the intake was increased by 1000 calories during the second part. The potassium balance was approximately 0 during this period.

Except for the first three days of the experiment, the sodium balances remained positive to a variable degree throughout.

Experiment 2. A patient, W. C. (aged 34), also was studied in the hospital. Nine years previously, he had accidentally shot himself while cleaning his gun. The bullet perforated the ileum and this area had to be resected. Three years later he began to have persistent diarrhea and to lose weight rapidly. A diagnosis of regional ileitis was made and, subsequently, an ileotransverse colostomy was done. He improved temporarily, but, two years before the present admission, he had a recurrence of complaints. A further resection of his ileum was performed at the previous anastomosis and an ileocecostomy was established. Following the most recent operation he again improved temporarily but was unable to retain the weight he had gained. His diarrhea persisted with alternate remissions and exacerbations. The experiment consisted of four periods, as follows:

Periods I and II represent control periods and total ten days. During

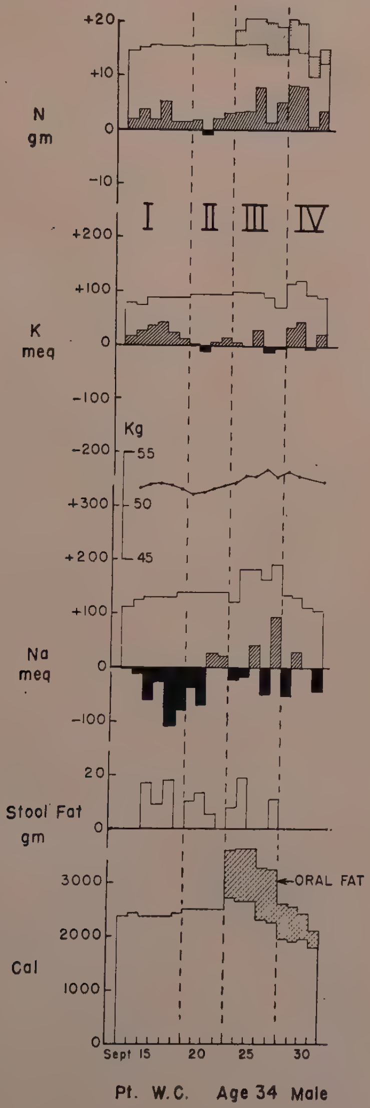

FIGURE 2. Metabolic Chart of Patient W. C. Use of oral fat emulsion as a caloric supplement in the nutritional repletion of a patient with regional ileitis.

this time, intakes remained virtually constant at approximately 2400 calories and 15 grams of nitrogen per day.

Period III lasted five days and, during this time, the protein intake was supplemented by means of an orally administered protein hydrolysate. This added about 6 grams of nitrogen per day to the intake. At the same time, the caloric intake was supplemented by means of oral fat emulsion. This increased the energy intake by approximately 1000 calories per day.

Period IV lasted four days. An attempt was made to keep the intake constant except for substitution of an equivalent amount of whole-protein supplement for the protein hydrolysate. Unfortunately, it was not possible to keep the intakes constant, as planned, because the patient reacted poorly to administration of barium in the course of some x-ray studies of his gastrointestinal tract.

Results (See FIGURE 2). Periods I and II were characterized by minor fluctuations in the patient's weight and a persistently positive nitrogen balance which averaged 2.15 grams per day. Total stool fat was determined for three consecutive days in both periods. These values were used as controls for the stool fats determined while oral fat emulsion was being added to the diet.

Sodium balances were generally negative during periods I and II. The potassium balance tended to parallel the nitrogen balance.

In Period III both the caloric and nitrogen intakes were higher than in Periods I and II, and this was associated with a significant increase in nitrogen retention. The positive nitrogen balance averaged 5.3 grams per day. During this time, the subject gained approximately a kilogram and, in spite of the increased intake of dietary fat, failed to show any striking increase over control values in stool fat.

Period IV is noteworthy because the drop in caloric intake to control levels was not associated with a corresponding decrease in nitrogen retention. The average nitrogen retention per day during Period IV was the same as in Period III. Yet, in spite of the continuing protein anabolism, his weight began to decline slowly.

Values for stool nitrogens throughout the course of the experiment averaged three grams per day. Total stool fats, based on nine determinations on 24-hour samples, averaged 12.3 grams per day. This was in contrast to the average of 2.15 grams per day in the stools of normal volunteer subjects.

Discussion

Experiment 1 was planned originally as a study of the metabolic effects of intravenously administered fat. When this plan could not be carried out, oral fat was used as the source of supplementary calories instead. However, the problems involved were similar, since, in each case, it was important to appraise the metabolic effects of relatively large quantities of fat added to submaintenance diets, and to determine whether the protein-sparing qualities of such amounts of fat were in accord with what might be predicted from the isodynamic law.

In Periods II and III of experiment 1, the effect of supplementary carbohydrate on nitrogen balance may be compared to that of a calorically equivalent amount of fat. Since the periods are not long enough, it cannot be concluded that supplementary fat is actually superior to supplementary carbohydrate with respect to protein sparing. On the other hand, it is quite clear that the supplementary carbohydrate does not do a better job of "sparing" protein than does fat.

The fact that the nitrogen balance does not become more positive in the last part of Period III, when the caloric intake is further increased, suggests that, in this instance, the level of nitrogen intake may have become a limiting factor in the utilization of protein.

Early in their development, it was recognized that oral fat emulsions would find their principal use as supplements, either to raise the energy content of diets to requirement levels, or for purposes of hyperalimentation. Besides being an extremely concentrated source of calories, oral fat emulsions may have the additional virtue of decreasing only gradually the intake of other nutrients in the diet. Mayer and Bates[18] have shown, in animals, that induced increases in blood sugar, within physiologic limits, diminish energy intake. Since fat influences blood sugar only indirectly, and certainly less than do protein and carbohydrate, the inhibitory effect of supplementary fat on the intake of other foods should be minimal. Thus, if excessive delay in gastric emptying can be avoided, such emulsions should constitute an ideal caloric supplement for persons whose dietary intake is limited by a poor appetite or by mechanical inability to tolerate food in bulk.

Experiment 2 represents an attempt to assess the impact of hyperalimentation on the nutritional status of a patient with a limited small bowel area. It was hoped that by "mass action" increased absorption of nutrients would take place. This apparently occurred. There was no accentuation of the diarrhea when the protein and fat contents of the diet were increased; indeed, the patient felt a great deal better. It was only when he began to feel ill as a result of ingestion of barium (for x-ray studies) that his intake fell off and his weight decreased.

Unfortunately, it was not possible to study utilization of the added protein after supplementation with oral fat emulsion had been discontinued. However, in Period IV there is a drop in caloric intake to control levels which is not associated with a corresponding decrease in nitrogen utilization. Due to the variables involved, it is not possible to explain this lack of sensitivity to changes in caloric intake. One explanation might be that the patient's protein stores were still depleted, thus rendering the nitrogen balances less responsive to variations in energy intake.

Summary and Conclusions

Metabolic studies, involving administration of an oral fat emulsion of high caloric value to a volunteer subject and to a patient, are described.

In the case of the volunteer, fat added to a diet inadequate in calories compared favorably in its nitrogen "sparing" properties to an equivalent amount of supplementary carbohydrate.

The marginal quantity of dietary protein given the volunteer subject appeared to be the limiting factor in protein utilization as the caloric intake was increased to successively higher levels by means of the oral fat supplement.

Oral fat emulsion proved to be an effective caloric supplement, judged by weight gain and nitrogen retention, in the nutritional repletion of a patient with intestinal insufficiency due to repeated resections of the small bowel.

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ORAL FAT EMULSIONS IN THE FEEDING OF PATIENTS WITH SEVERE BURNS*

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In recent years, there has been considerable interest in the metabolic and nutritional problems associated with serious burns. Disturbances have been observed in the metabolism of all nutrients studied so far. In general, the abnormalities are related to the severity of the injury and to the status of the individual (age, sex, nutrition, etc.) at the time of injury. Only minor nutritional problems are encountered in patients, previously in good health, with superficial second-degree burns. In contrast, patients with deep second-degree or third-degree burns may present some of the most difficult nutritional problems. Sloughing (or excision) of the dead skin, followed by granulation of the uninjured deeper tissue must occur in deep burns which involve the entire thickness of the skin. If the granulation area is of any significant size, skin coverage cannot take place spontaneously, and skin grafting must be performed. If the patient is maintained in a good nutritional state, granulation tissue appears firm, red, and healthy; infection can be controlled; skin grafts take well; and donor sites heal uneventfully. However, if the patient with deep burns becomes malnourished, serious complications ensue. Wound healing is delayed, infection is more serious, and convalescence is prolonged. Granulations in such patients are soggy, gray, and extremely friable, or, at times, absent. Skin grafts do not take over such areas, nor do donor sites heal in such patients.

The pathogenesis of the nutritional depletion seen following severe burns is not completely understood, but it is clear that inadequate food intake is one of the important etiologic factors. We know, in a general way, that the dietary requirements of the severely burned adult patient are higher than those of normal individuals. But we do not know how much higher and, specifically, what the quantitative relationships of the various metabolites should be. Nor do we know the optimal timing for the feeding regimens except that, as a generality, feedings should be started early.

We are currently investigating some of these problems. The patients are cared for on metabolic wards. Whole blood, dextran, and electrolytes are used when indicated as replacement therapy during the first day or two following injury. Occasional blood tranfusions are given later if anemia develops. The burns are usually dressed with firm dressings, either dry or with various ointments. Operative procedures are generally carried out under pentothal and nitrous oxide, or cyclopropane anesthesia. Several antibiotics, singly and in combination, are used in the prophylaxis and treatment of infections.

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In addition to observations of clinical course, wound healing, *etc.*, serial measurements are made of body weight, nitrogen, sodium, potassium, and caloric intakes; and urinary and fecal nitrogen, sodium, and potassium outputs. In most patients, frequent measurements of liver function (serum bilirubin, thymol turbidity and flocculation, cephalin flocculation, prothrombin time, and bromsulfalein retention), plasma volume, circulating plasma proteins and hemoglobin, and various hematologic indices are also made.

The food for the patients is prepared in a special research diet kitchen. We depend entirely on liquid feedings. Some of the advantages of liquid feedings are as follows: a high intake can be provided in a comparatively small volume; constancy of composition is more nearly assured than by the usual solid diets; and liquid diets are easier to formulate, prepare, serve, record, and calculate. In addition, some patients have severe burns of the face and, under this circumstance, liquid feedings are much more readily and easily ingested than solid food.

The compositions of some of the diets we have been evaluating in adult patients are listed in TABLE 1. All diets are calculated on a per-kilogram body-weight basis. Fat emulsions* have been used as the chief source of fat in the feedings of forty patients studied metabolically during the past two years. The fat emulsions have not been fed alone as supplements, but always as part of feeding mixtures. Some representative diets are listed in the case reports. The fat emulsions have proved very useful because of their stability, easy incorporation into formulas, minimal separation, relative blandness, good digestibility and tolerance, and high acceptability. The percentage of calories from fat has been 25–50 per cent of the total calories. This level is higher than had been previously thought advisable for the seriously burned patient, but we have not noted any ill effects specifically attributable to this factor.

TABLE 1

REPRESENTATIVE LIQUID FEEDINGS*

Protein per kilogram body weight, grams	*Calories per kilogram*	*Protein, grams*	*Carbohydrate, grams*	*Fat, grams*	*Total calories*	*Calories from fat, %*
1.0	35	70	390	68	2450	25
1.5	45	105	486	88	3150	25
2.0	50	140	341	175	3500	45
4.0	45	280	311	88	3150	25
4.0	67	280	285	271	4700	52
4.5	78	315	442	270	5460	46

* For a 70-kilograms adult.

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* Lipomul was furnished by Dr. Earl L. Burbidge of the Upjohn Company, Kalamazoo, Michigan. Preparation No. 375-1 furnished by Dr. Warren M. Cox, Jr. of Mead Johnson and Company, as well as a fat emulsion prepared at the Medical College of Virginia were used in some patients.

Data obtained in children suggest that, in general, if dietary intakes at levels comparable to those considered optimal for normal children of similar age, six, and weight are begun early after thermal injury, and are continued throughout convalescence, satisfactory nutrition will be maintained. This is illustrated by the following case report.

Case 1. Patient L. H., a six-year-old colored boy, was in good health and in excellent nutritional status at the time he sustained a flame burn involving 25 per cent of his body surface as full-thickness burn and 17 per cent as partial-thickness burn (total burn, 42 per cent). He was started on a liquid diet the day after injury and, during the first week, his intake was gradually increased to a level of 2.5 grams protein and 85 calories per kilogram body weight daily (these are the levels suggested by the National Research Council Food and Nutrition Board as optimal for a normal male child of this patient's age and weight). Twenty-five per cent of the calories were supplied by fat in an emulsified form. Vitamin A, thiamin, riboflavin, niacin, and vitamin D were supplied at a level of three times the levels recommended for normal children of the patient's age and weight by the Food and Nutrition Board of the National Research Council. Ascorbic acid was given at ten times this level. In addition, 30 cc. of oral crude liver extract* were given daily. These feedings were readily ingested and well tolerated. During the first three weeks, he lost three kilograms in weight, an amount equal to 13 per cent of his admission weight (see FIGURE 1). Thereafter, he was in apparent positive nitrogen balance, and gained weight progressively, so that he regained his admission weight by the ninth week. His clinical course was uncomplicated, sloughing of the deep burn had occurred by the third week, and the granulations were firm and healthy in appearance. He was successfully grafted in stages and the donor sites healed rapidly. By the 14th week, he was 13 per cent above his admission weight, and left the hospital in excellent physical and nutritional status.

The nutritional requirements of adult patients with serious thermal burns have not been established. Our data indicate that these requirements are quantitatively greater than those of uninjured normals. In general, female adult patients, previously in good health and in good nutritional status, remain in fairly good nutritional status when maintained on dietary intakes of 1.5–4.0 grams protein and 45 calories per kilogram body weight. Twenty-five per cent of the calories have been supplied in these feedings by emulsified fat. Patients with burns involving 30 per cent or more of the body surface, chiefly deep, may lose a moderate amount of weight, both of body fat and body protein, at these levels, but less, we feel, than if lower dietary levels are maintained. Young adult male patients are apt to present more difficult nutritional problems than females. If the caloric intake is raised to 60–70 calories per kilogram body weight in the anabolic period by means of oral emulsified fat, an increase in nitrogen retention and an accelerated gain in body weight ensue. At these elevated caloric levels, 45–50 per cent

* Product of The Valentine Company, Inc., Richmond, Va.

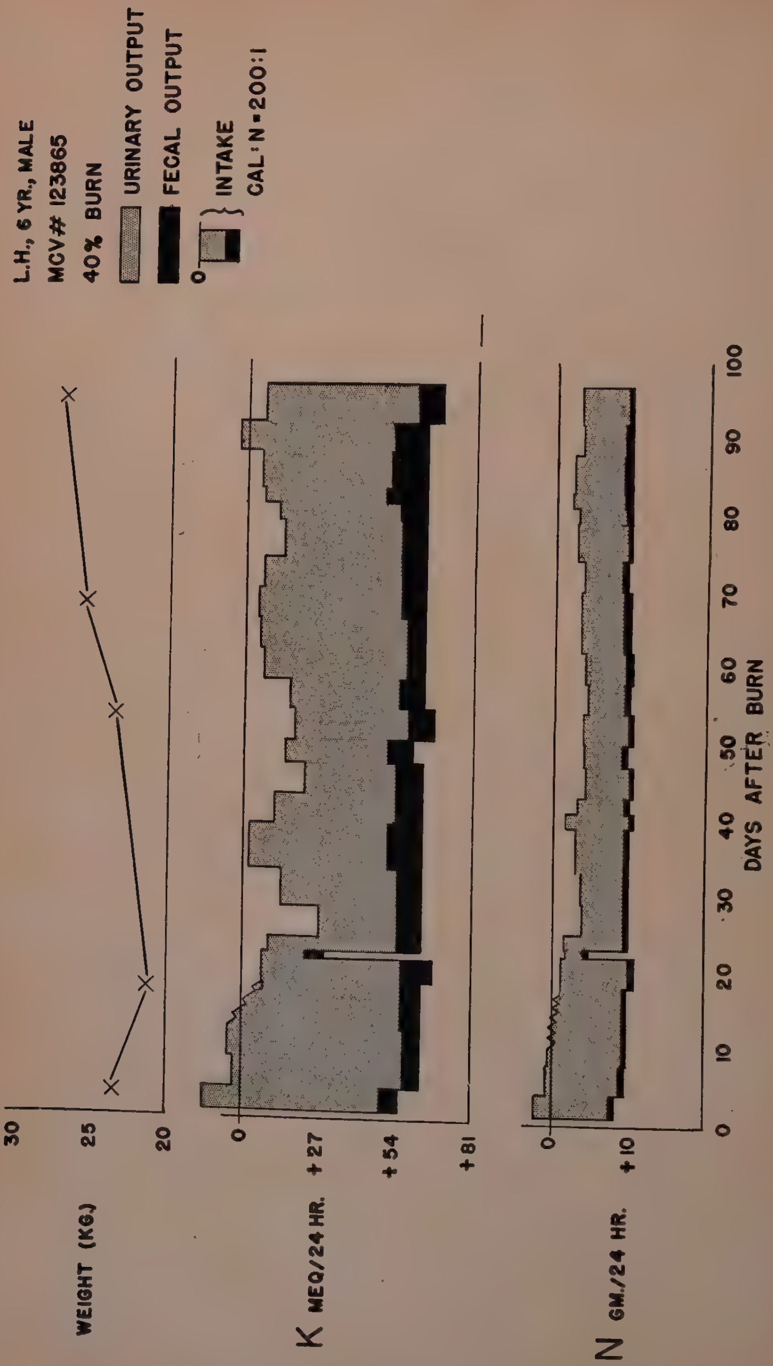

Figure 1. Nitrogen and potassium metabolism following burns.

of the total calories have been supplied by emulsified fat. Some of these points are illustrated in the following case reports.

Case 2. Patient E. M., a 20-year-old Negress, was well nourished and in good health at the time she sustained a flame burn which involved 48 per cent of the body surface. Approximately 25 per cent of the burn was third degree. She was three months pregnant at this time. Oral dietary intake was begun the day of injury and by the second day she was ingesting 215 grams protein and 2400 calories per day. This amounted to a daily intake of four grams protein and 45 calories per kilogram of her admission body weight. Twenty-five per cent of the calories were supplied by fat as an emulsion. She was in apparent mild negative nitrogen balance only for a brief period (days 9–16) post injury. She gained weight progressively, so that by the third week she weighed about three kilograms more than at the time of her admission. The dermal burn healed uneventfully. The deep burn sloughed by the sixth week, and the granulations were firm and pink. Skin grafting was carried out successfully in stages, and the donor sites healed normally. Skin grafting had been delayed because it had not been possible to distinguish with assurance the deep-dermal from the full-thickness burn. By the tenth week she was essentially healed, had gained five kilograms in body weight, and was in good physical and nutritional status. Her pregnancy was proceeding normally. At this time, she was in nitrogen equilibrium on a daily intake of 215 grams protein and 2400 calories. After 14 days of control observations, the protein intake was kept constant, but the caloric intake was raised to 3700 over a period of four days and then maintained at this level for the next three

TABLE 2

LIQUID FEEDING FOR PATIENT* WITH BURNS

Ingredients	*Amount, grams*	*Protein, grams*	*Fat, grams*	*Carbohydrate, grams*
Eggs (raw)	100	11	10	1
Peanut butter	120	31	57	25
Somagen	165	116	—	36
Egg albumen (dried)	75	55	—	5
Dextri-maltose	140	—	—	138
Crude liver extract	30	1	—	—
Fat emulsion	350	—	140	35
Total	—	214	207	240
Calories (3,680 total)	—	855	1865	960
Calories, %	—	23	51	26

Vitamins (totals):

A	30,000 I.U.	Riboflavin	14 mg.
D	1,300 I.U.	Niacin	90 mg.
Thiamin	8 mg.	Ascorbic acid	1,300 mg.

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* E. M., 21-year-old pregnant female; admission weight, 54 kg.; 48% burn.

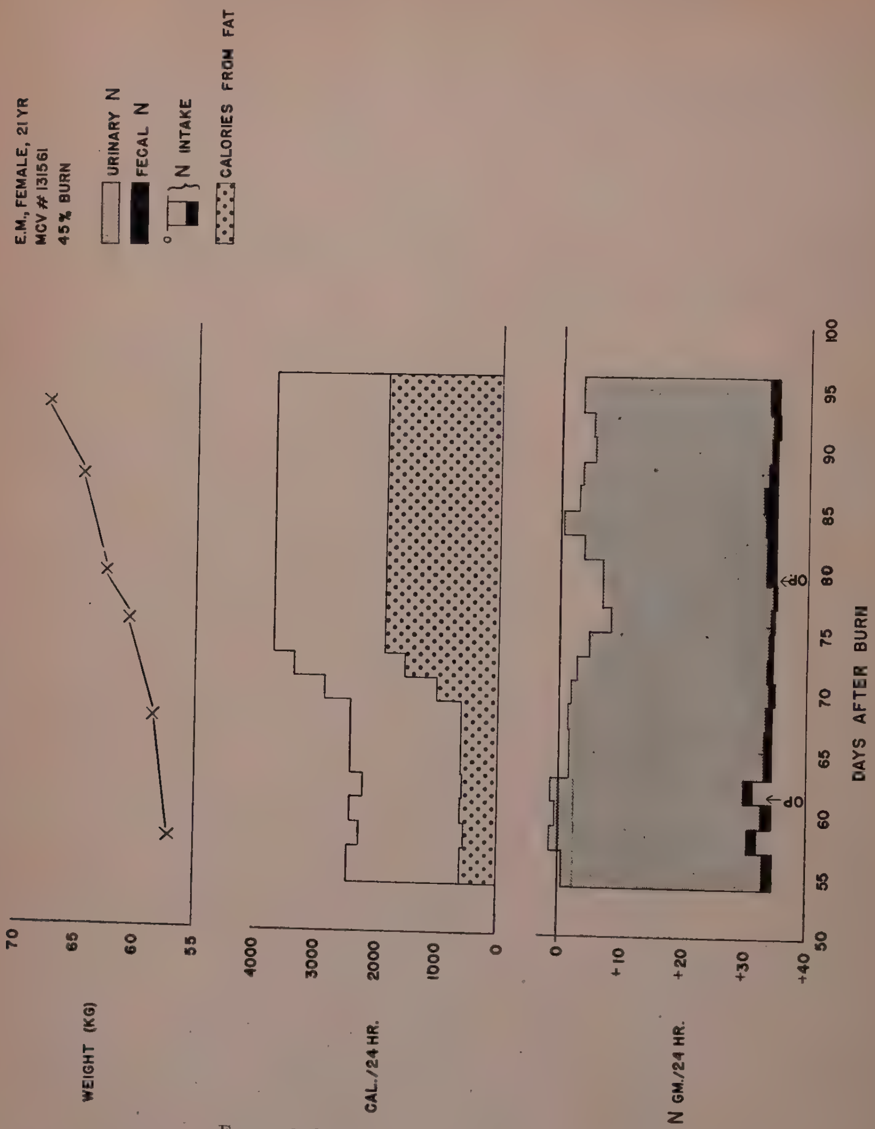


FIGURE 2. Nitrogen metabolism following burns.

weeks. The additional 1300 calories were provided wholly by emulsified fat. Fifty per cent of the total calories were thus supplied by fat at the elevated caloric levels. There were no changes in gastrointestinal or liver function. The patient promptly went into positive nitrogen balance of about five grams per day and gained weight at an accelerated rate (see FIGURE 2, TABLE 2).

Case 3. Patient J. A., a 41-year-old Negro, was well nourished and in good health at the time he sustained a flame burn involving 35 per cent of his body surface. Almost the entire burn was deep third degree. He was admitted on the third day following injury and was started immediately on a liquid diet which supplied 285 grams protein and 3200 calories daily. This was based on a calculated intake of 4 grams protein and 45 calories per kilogram of his admission body weight. Twenty-five per cent of the calories were from fat. His dietary intake was essentially constant at this level for the next six weeks. Despite the high-protein diet, he was in negative nitrogen balance during the first six weeks following injury. The daily urinary nitrogen excretion was about 48-52 grams, and the daily fecal nitrogen about two grams. Since the total nitrogen intake was about 46 grams daily, the apparent negative nitrogen balance was four to eight grams daily. During the first six weeks he lost about 9.5 kilograms in weight, an amount equivalent to 14 per cent of his admission weight. The deeply burned area (30 per cent of his body surface) had sloughed by this time. The loss of the very deeply burned skin and subcutaneous tissue accounted for a significant part of the observed weight loss. Beginning on the 42nd day the caloric intake was increased over a period of three days from 3200 to 4250. The additional calories were supplied wholly by emulsified fat; protein and carbohydrate intakes were kept constant. Nineteen hundred calories, or 45 per cent of the total, were thereby supplied by fat at the increased caloric level. The composition of this diet is listed in TABLE 3. The patient tolerated the feedings very well; there was no nausea, vomiting, distention, constipation, or diarrhea.

TABLE 3

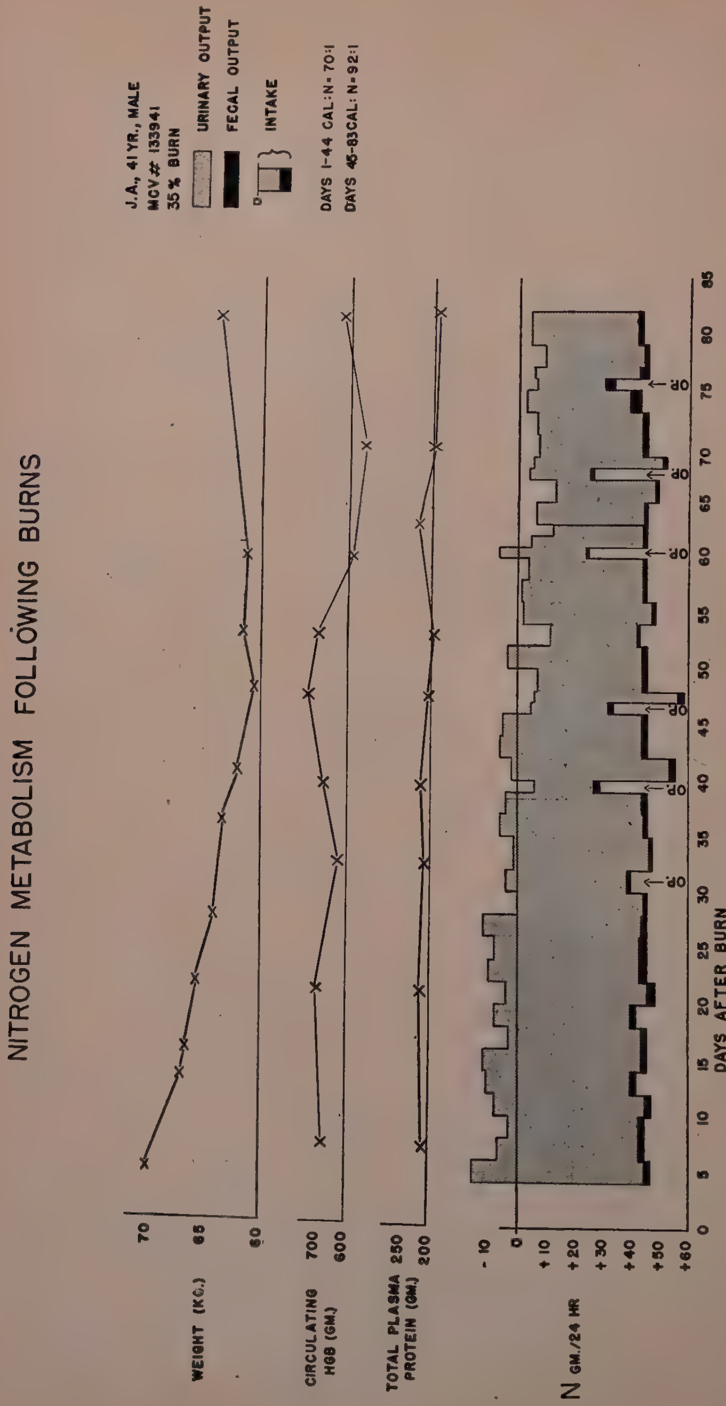
LIQUID FEEDING FOR PATIENT* WITH BURNS

Ingredients	*Amount, grams*	*Protein, grams*	*Fat grams*	*Carbohydrate, grams*
Eggs (raw)	100	11	10	1
Peanut butter	165	43	79	35
Somagen	225	158	—	50
Egg albumen (dried)	100	74	—	6
Dextri-maltose	195	—	—	193
Crude liver extract	30	1	—	—
Fat emulsion	295	—	118	30
Total	—	287	207	315
Calories (4,275 total)	—	1,150	1,865	1,260
Calories, %	—	27	44	29

Vitamins (totals):

A	26,000 I.U.	Riboflavin	18 mg.
D	1,300 I.U.	Niacin	115 mg.
Thiamin	11 mg.	Ascorbic acid	1,000 mg.

* J. A., 41-year-old male; weight, 71 kg.; 35% burn.


NITROGEN METABOLISM FOLLOWING BURNS
J.A., 41 YR., MALE
MCV # 133941
35 % BURN
URINARY OUTPUT
FECAL OUTPUT
INTAKE
0
DAYS 1-44 CAL:N = 70:1
DAYS 45-83 CAL:N = 92:1
WEIGHT (KG.)
70
65
60
CIRCULATING HGB (GM.)
700
600
TOTAL PLASMA PROTEIN (GM.)
250
200
N GM./24 HR
- 10
0
+ 10
+ 20
+ 30
+ 40
+ 50
+ 60
OP.
OP.
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0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
DAYS AFTER BURN

Figure 3.

His nitrogen balance became slightly positive in the first five days on the increased caloric level, but then became slightly negative again for four days. This latter state was associated with the occurrence of glycosuria. The glycosuria and associated hyperglycemia were readily controlled with relatively small amounts of regular insulin, and the patient went into increasing and sustained positive nitrogen balance of about five grams daily. No changes in liver function were observed during the period of increased caloric intake. He gradually gained weight and felt stronger. The appearance of his wounds improved; the granulation tissue became firm and pink. Skin grafting was successfully carried out, and the donor sites healed uneventfully.

FAT INGESTION AND CHYLOMICRONS

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The blood of man and of animals, when viewed with the dark-field microscope, shows numerous small particles with Brownian movement, which Gage has named *chylomicrons.*[1] They average approximately 0.5 micron in diameter, and stains indicate that they consist largely of neutral fat. These particles can be counted with reasonable ease and accuracy and show rather typical curves during absorption of fats, but not during absorption of carbohydrates or proteins or of both together.[1] Repeated tests on the same subject demonstrated that chylomicron curves remained about the same in each individual.[5]

Besides the chylomicrons, there are smaller particles in the blood, visible in the dark-field microscope as small spots or shadows. These small chylomicrons we prefer to call *lipomicrons.*[2] Lipomicrons can not be counted easily, and the smallest ones cannot be counted at all, but their relative concentration can be estimated with the nephelometer (Tyndal effect). A few authors have proposed to measure chylomicrons with the colorimeter or with the nephelometer.[3-7] We believe that this is not possible[2] because turbidometric and nephelometric determinations measure chylomicrons, lipomicrons, and a fraction of macromolecules such as have been described by Gofman's group.[8]

Although observations on chylomicrons and lipomicrons cannot replace fat-balance studies, they are of great interest, because they tell us about mechanisms of absorption, transportation, and disposition of fat, which cannot be studied otherwise. Their concentration in the blood has been studied in diseases, like sprue,[9-11] diabetes,[12] and atherosclerosis.[2-5, 13, 14]

Chylomicrons in the blood have been considered to be identical with the finely dispersed fat appearing in the small intestine and in the lymphatics during digestion. However, Frazer [15-18] has demonstrated distinct physical differences between the two types of fat particles. It appears that the chylomicrons obtain a stabilizing surface film upon entering the bloodstream.

Chylomicrons are considered to consist of neutral fat with an outside shell of protein [15-20] and/or of lecithin, with bile salts playing some role.[18, 21] Moreton [3-5] assumed that they contain cholesterol, Gofman[22] stated that they contained five per cent cholesterol, and Swank and Wilmot found three per cent by indirect methods.[23] After obtaining concentrated chylomicrons which were separated from blood-bank plasma,[2] we have been able to answer this question more definitely. The concentrated chylomicron cream is white, has the physical appearance of oleomargarine, and a slight but distinct taste of butter. When exposed to air, it turns yellow. The chylomicrons were found to consist approximately of 80 per cent triglycerides and 20 per cent free sterols, sterol esters, and a yellow substance with the properties of an unsaturated complex hydrocarbon. Of the sterol fraction, 80 per cent appeared to be cholesterol, 65 per cent of which was esterified. We suspect a small part of the sterol fraction to consist of hormonal sterols. Thus, chylomicrons may contain up to 15 per cent of cholesterol, which is considerable in view of the inertness of that substance when compared to neutral fats. Ether and chloroform extracts of chylomicron fat did not contain phosphorus, excluding the presence of such substances as lecithin, cephalin, or sphingomyelin. The aqueous residue left after ether extraction contained considerable quantities of sulphur and phosphorus. This residue was very mucilaginous, and we believe that it may be the material which coats the surface of the chylomicron and gives it its unusual stability. We have found that concentrates of chylomicrons can be dispersed easily after prolonged centrifugation and after long standing, and still give the appearance of a normal chylomicron concentration in the dark-field microscope. We are interested in this substance because, having access to large amounts of chylomicron fat, we may be able to find and identify a natural stabilizer for oral or intravenous fat emulsions. The saponification number of human chylomicron fat was found to be 185,[2] while that of human depot fat has been reported to be between 195 and 198.[24] Deposition of fat in the depots appears to parallel the chylomicron curve.[1]

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* In this review the work of my research group is presented largely, and I want to give due credit to Drs. G. Becker, R. Greenspan, L. Marder, B. Maizel, E. Levy, and Mr. S. Kraft.

The origin of the chylomicrons is closely connected with the topic of this conference, "The Use of Oral Fat Emulsions." I concur with Frazer[15–17] in the dual mechanism of fat absorption. In the upper small intestine, some fat is partially hydrolyzed, and all fat is dispersed spontaneously into a fine emulsion. Part of this emulsion, probably the long chain fats, having a negative charge, [15–18] enter into fine channels in the epithelium[25] of the upper small intestine, [15–18] are drawn into lymph channels with the help of the pumping action of the villi, and pass through the thoracic duct into the blood stream. Choline and methionine may play a role in this absorption.[15–18, 26] The other fraction of the fatty chyme, probably the short-chain fats, is hydrolyzed completely, and absorbed in the lower small intestine.[15–18] The fatty acids are absorbed by polar effects into the epithelium,[15–18] phosphorylated,[27, 28] and there re-synthetized into neutral fats. They are transported largely to the liver with the portal blood. It is possible that, in the peculiar "nests" of Mall,[24] some of the fat of the portal blood enters into lymphatic ducts, or *vice versa*. Although we have learned a few things about the balance between these two processes of fat absorption, we are just at the beginning.

An important consideration in the study of fat absorption and its partition mechanism is the excretion of fats and cholesterol into the intestinal tract. Normally, most of these fats and cholesterol are re-absorbed. Attempts to prevent the re-absorption of cholesterol in the treatment of arteriosclerosis are being made in the Cardiovascular Department of our Institute.[31]

Oversecretion of fatty material and steatorrhea have been reported in patients with hepatic cirrhosis. In these patients, fat absorption did not appear to be impaired, and the increased excretion of fat was not diminished with a fat-free diet.[30]

It seems that the stability of oral fat emulsions is of great importance in the problem of fat absorption. Because stability in the test tube does not necessarily indicate stability in the stomach and intestine, this question has to be studied with intubation of the small intestine. I have discussed this aspect with Dr. A. C. Frazer, who believes that some results contradicting his findings[32-34] may have been due to instability of the fat emulsion used. Finely emulsified and stable preparations of paraffin oil are absorbed as well as finely emulsified triglycerides.[15-18]

We have found that, in persons over 60 years of age, serum lipase and pancreatic lipase are diminished significantly.[35, 36] This finding gave us the lead to study chylomicrons in the aged. In repeated series of experiments, we have found that fat absorption in aged persons differs from that in young ones.[2, 13, 14, 37] Following a standard fat meal, subjects over 60 years of age have higher peaks of chylomicrons and a more prolonged chylomicronemia. Nephelometer determinations, done at the same time as the chylomicron counts, indicate that lipomicrons do not increase significantly in old people over young ones, and that, in the aged, the increase in corpuscular fat in the blood consists largely of chylomicrons. Interestingly, we find that in aged diabetics the reverse is true. They have distinctly more lipomicrons and approximately the same degree of chylomicronemia, when compared to a nondiabetic group of older individuals.[12]

I do not believe that the difference between normal old and young persons is related to differences in activity. As explained above, nephelometric measurement of chylomicrons in the aged[7] is misleading. The chylomicronemia in the aged appears not to be related to differences in the disposition of chylomicrons in young and old subjects, as is indicated by chylomicron curves following intravenous injection of plasma rich in chylomicrons.[37]

In the aged group of subjects, addition of lipase to the fat meal apparently improved a deficiency of lipase and thereby changed conditions of absorption. Lipase depressed chylomicronemia, but had little effect on the lipomicrons, as demonstrated by nephelometry. In the group of young subjects, an optimal system of lipase digestion apparently was not increased by additional lipase.[37]

Tween 80, an emulsifier (polyoxyalkalene sorbitan monooleate), when given with the standard fat meal to aged subjects, had a similar effect as lipase on the chylomicron curves, although not as pronounced. On the other hand, Tween 80 elevated the chylomicron curve of young subjects considerably, contrary to all expectations.[37] The latter observation is important in view of the present argument about synthetic *versus* natural shortening in the baking industry, as well as in view of the use by some laboratories of Tweens for oral or intravenous fat emulsions. Tween 80 and Triton A 20 (an arylalkylpolyether of phenol) were injected intravenously into rabbits by Kellner, *et al.*[38] Hyperlipemia followed regularly, and a considerable elevation of blood cholesterol was observed. The hyperlipemia following Tween 80 disappeared within 24–48 hours; that following Triton A 20 lasted for 5–15 days. Tween 80, when fed to rabbits on a normal diet, did not affect blood-cholesterol levels. When fed to rabbits on a high cholesterol diet, however, it augmented the hypercholesterolemia usually produced by cholesterol diets, possibly by increasing intestinal absorption of cholesterol, and it accelerated the appearance of atherosclerotic lesions.[39] On the other hand, while intravenous injections of Tween 80 or Triton A 20 led to increase of blood cholesterol and phospholipids in rabbits on a cholesterol diet, the animals had much less atherosclerosis than the control rabbits fed cholesterol. Nevertheless, repeated intravenous injections of Tween 80 did not diminish the degree of atherosclerosis previously induced.[40, 41] These observations may be related to those of Ahrens and Kunkel[21] because, in the latter two groups of rabbits, the phospholipid-cholesterol ratio was above one.

Fatty acids stimulate secretion of mucus, and we suspect some detergents to have a similar effect. Frazer, *et al.*[60] have shown that such mucigogue effects of fatty acid lead to precipitation and clumping of barium in the intestine, producing the appearance of a deficiency pattern. We are studying this question in aged subjects.

In a patient with hyperlipemia (male, 46 years, total lipids 1500 mg. per cent, cholesterol 500 mg. per cent, clear serum, xanthomatosis, fatty liver), chylomicron counts were depressed following administration of lipase with the fat meal.[9] It appears that alimentary hyperlipemia is superimposed on a persistent metabolic chylomicronemia.[5]

Very little corpuscular fat, as indicated by chylomicron curves, is absorbed in cases of nontropical sprue, of which we have studied a few. Lipase and Tween 80 did not change the chylomicron curves appreciably.[9] This observation is in agreement with Frazer's experience.[11, 18, 42] Jones, *et al.*[43] have reported reduction of fecal fat following administration of Tween 80 to patients with subtotal gastrectomy. In one case of sprue treated with Tween 80 by mouth, the patient gained weight. Black and Simpson[44] found increased fat absorption in cases of tropical sprue when large doses (ten grams) of sodium glycerophosphate were administered with the fat meal. Fourman's results with tropical sprue[10] indicate variable chylomicron responses. ACTH and cortisone appear to affect fat absorption in cases of sprue.[45, 46] Their effects on the partition of fat absorption should be studied.

Apparently, chylomicrons can arise from fat mobilized from the fat depots, evidently for the supply of energy. We have observed a low level of chylomicrons in the peripheral blood during fasting. Gage and Fish[1] have demonstrated that there are hardly any chylomicrons in the blood during a prolonged fast of six days but that, following vigorous physical exercise, the counts went up and showed regular peaks like those following a fatty meal. Frazer has shown similar peaks during prolonged fasting, apparently not related to physical exertion.[15-17] Both authors assumed that these sudden elevations of chylomicrons were due to fat mobilized from the depots for the needs of the body. We know that mobilization of depot fat is under the control of autonomic nerves, most probably the sympathetic nerves,[47] and that we may thus have the means of stimulating or blocking mobilization of fat from the depots. We have studied the effects of rest and exercise in a group of six young subjects. The chylomicrograph area of tests with exercise was increased definitely in one subject, showed no change in two, and a decrease in two.[48]

The principal source of chylomicrons appears to be absorbed fat. In this case, their number will depend upon the factors which rule the partition of fat, namely, absorption into the portal vein and into the lymphatics, respectively. Secondly, chylomicrons may be due to re-absorption of fat excreted previously into the intestine. Thirdly, chylomicrons may be derived from fat mobilized from the depots. The height of chylomicronemia at any time depends upon supply from these sources and upon the disposition of chylomicrons in the blood, the liver, the fat depots, and tissues. Thus, variations in the degree of chylomicronemia may be due to a number of reasons. Others[15-18] and we ourselves[2, 48] have ruled out the duration of gastric emptying following meals with moderate amounts of fat, as affecting the degree of chylomicronemia. Moreover, there was no difference in gastric emptying times of fat barium meals performed in experiments with exercise or smoking.[48] The difference in fat available from depots in different individuals, however, may explain differences observed by us in response to resting, exercise, and smoking.[48] We find that, during exercise as well as during smoking, the chylomicron curves showed very definite changes in the time incidence of the peaks, as well as deviations from the resting values. Individual variations may be due to emotions, as pointed out early by Gage and Fish[1] and by our selves,[2, 13, 14, 37, 48] and possibly to nausea.[48] Availability of mobilizable fat from depots may play a role. Since the mobilization of fat from depots is largely under the influence of sympathetic nerves it is easy to see how emotions, smoking, and exercise are able to affect it, the incidence and variability of response depending on the response of the sympathetic-adrenal system. In trying to analyze a phenomenon like chylomicrons (or any other phenomenon), we must not try to simplify, but rather try to follow it into its ramifications.

Recent work from Gofman's laboratory[49] indicates that, under the influence of heparin, the larger lipoproteins (Sf 20-70) as well as the smaller lipoproteins (Sf 10-20) are transformed into smaller molecules. The smaller molecules appear to be different chemically from the larger ones. Thus, it seems likely that a degradation of the lipoproteins in the blood can occur. It is quite possible that such process occurs naturally either without heparin or, possibly, with the help of heparin produced in the body. It has been shown by Hahn[50] and others [23, 51-55] that heparin, given intravenously, makes chylomicrons disappear, partly or entirely, from the circulating blood. Thus, it appears possible that chylomicrons are absorbed during digestion from the intestine, and that they disappear by transformation into smaller molecules, down to and below the Sf 10-20 molecules which Gofman considers of importance in the causation of atherosclerosis. It is conjectural whether the 15 per cent cholesterol content of the chylomicrons contributes to the level of blood cholesterol and cholesterol esters. It may constitute an important source of exogenous cholesterol. An effect of heparin in increasing the rate of fat absorption from the intestine has been reported.[56]

I have made a rough calculation of the total amount of chylomicrons in the blood and of their cholesterol content, and I am presenting it for what it may be worth. The calculation is based on an estimation by Gage[1] that one cu.mm. of blood contains approximately 80 million chylomicrons. Assuming a diameter of 0.5 micron, an adult person with five liters of blood (50–60 kg. bodyweight) would have 25 ml. of chylomicrons, *i.e.*, 22.5 grams. These would contain, according to our data,[2] 22.5 grams of total lipids. The total lipids would consist of 18 grams of triglycerides, and 4.5 grams of sterols, of which 3.6 grams is cholesterol, and 0.9 grams other sterols.

Cholesterol has been held responsible for the causation of atherosclerosis in man and in animals. However, the approach to explain this phenomenon has varied. The main theories appear to me as follows:

(1) A diet high in cholesterol leads to increased cholesterol content of the blood and infiltration and deposition of cholesterol in arteries.[57]

(2) Macromolecular substances may form a film over the intima, and prevent proper oxygen supply to the intima and sub-intima, leading to necrosis and deposition of calcium and cholesterol.[58, 59]

(3) Large lipoprotein molecules, of the size of Sf 10-20, have been correlated with coronary infarcts and atherosclerosis, and may play some role there, although the mechanism is not known.[8]

(4) Chylomicronemia following a fat meal is similar to that seen in pathological conditions with hyperlipemia.[5] Chylomicrons in the blood may be hammered into the fine pores of the intima with every pulse wave. The neutral fats are removed quickly, and cholesterol is slowly accumulated, acting as a foreign body, and giving rise to the sequence of atherosclerosis.[3-5, 13, 14]

Our findings of prolonged and increased chylomicronemia in the aged would fit into the latter theory. If this should be true, we would have to be cautious with administration of high-fat diets to older individuals over a prolonged period of time. Administration of lipase or suitable synthetic dispersing agents may overcome the high degree of chylomicronemia produced by fat in the diet of older people, but synthetic detergents should be used with discretion.

We find that increasing the amount of fat in the diet leads to a disproportionate increase in the degree of chylomicronemia.[2] The effects of smoking in certain individuals have been related to cardiovascular hypertensive and angiosclerotic disease. These observations may be explained, at least in part, by the fourth theory of arteriosclerosis.[2, 13, 48]

In review, I feel that we have touched only the beginnings, and that every problem we are working on breeds at least three new ones. *Ars longa, vita brevis.*

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THE USE OF ORAL FAT IN HYPERALIMENTATION AND PARENTERAL ALIMENTATION*

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It has long been known that maximum utilization of dietary proteins requires the presence in the diet of an adequate supply of nonprotein energy-producing foods, namely, carbohydrates and fats.[1] Fat has always been regarded as wholly interchangeable with carbohydrate as source of energy. Recently, however, impressive and pertinent data regarding the nutritional role of fats have been reported by Swift and co-workers,[2] who concluded that the presence of fat in the diet of rats confers "economy of utilization of food energy." Under conditions of caloric restriction, Swanson[3] has also found that fat exerts a profound body-sparing effect when it is included in protein-free diets fed to rats. The poor nitrogen balance of rats on low-fat rations was characterized by an increment in the relative concentration of blood urea and amino nitrogen. This change was associated with an increased urinary output of urea, ammonia, and amino nitrogen. The poor nitrogen balance and level of urea and ammonia output of rats were significantly reduced when the protein-free, low-fat, low-caloric diet was supplemented with methionine (4 mg. N day).

In earlier work, Pearson and Panzer[4] reported that weanling rats, fed *ad libitum* a complete diet lacking only in fat, gained 29 per cent less than rats fed diets containing eight per cent of corn oil or lard. A decreased fecal output of valine, lysine, and methionine, and a lower urinary excretion of lysine and methionine was found to occur in rats fed the fat-containing diets. In addition, in order to measure the effect of fat on tissue regeneration, protein-depleted adult rats were fed the fat-free diet and the diet containing eight per cent corn oil. The results, on the basis of weight gain and amino acid excretion, again favored the corn-oil-containing diet.

It is abundantly clear from the foregoing that fats play a heretofore unsuspected role in the protein metabolism of growing and protein-depleted mammals. This evidence, albeit derived from experimental animals, points to a metabolic as well as caloric need for an adequate intake of fat in patients whose protein stores have been depleted by disease or surgical procedures. Because of the physico-chemical properties of fats, their inclusion in therapeutic oral or intravenous mixtures has presented numerous technical difficulties. As a consequence of this fact, supplemental diets commonly employed have consisted almost entirely of carbohydrates and proteins. Some of these problems have now been resolved by the availability of a commercial fat emulsion. In this report we will describe some of our experiences with this product.

Nutritional Aspects of Steroid Therapy. In consideration of the now well-known catabolic effects of ACTH and cortisone, we felt it would be worth

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* These studies were supported by funds from the Office of Naval Research, Baxter Laboratories, Inc., and Sugar Research Foundation, Inc.

while to try to counteract the nitrogen, potassium, phosphate, and calcium losses induced by these drugs by appropriate dietary measures.[5] This led to the construction of a special synthetic diet of the composition shown in TABLE 1. The quantity of this diet given to each child was based upon the recommended allowances of the Food and Nutrition Board of the National Research Council. It is to be noted that this diet not only provides the major food stuffs in optimal caloric distribution, but that it also attempts to compensate for the calcium and potassium losses by the inclusion of calcium potassium lactate as a mineral supplement.

TABLE 1

COMPOSITION OF SYNTHETIC DIET*

Constituents	*Calories, %*
Milk proteins (mixtures of whole milk and Sheffield 60 per cent milk protein)	15
Lactose, U.S.P. (Sheffield)	50
Oral fat emulsion (Upjohn)	35
Total	100
Mineral supplement:	
Calcium potassium lactate, g./day	4
Vitamin supplements:	
Vitamin C, oz. orange juice/day	4
Vitamins A and D, oz. cod liver oil/day	0.7
Fluid supplement:	
Fruit juices and water, ml. fluid/cal.	1

* All diets supplied 2.0–3.0 grams of protein per kg. of body weight per day.

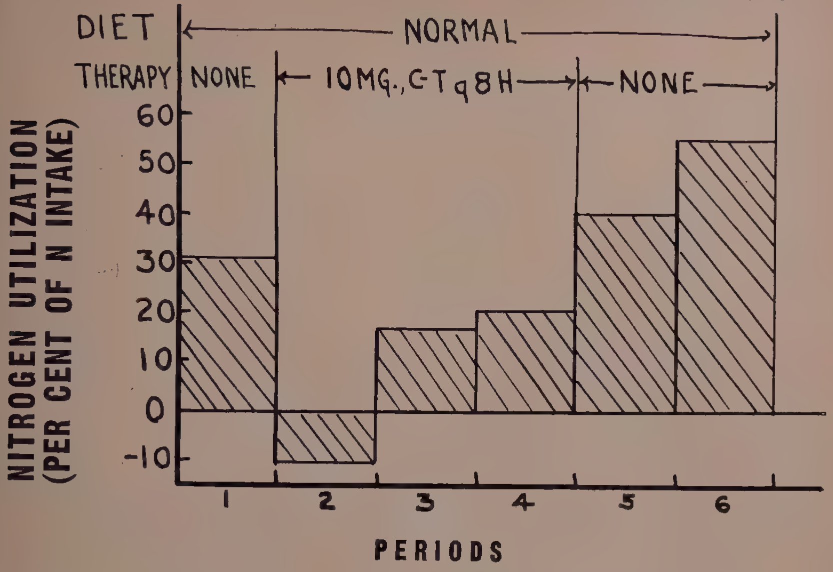
Flame photometer analyses of the blood and urine for potassium and sodium levels showed that this synthetic diet maintained electrolyte balance within normal levels throughout steroid treatment.

Typical results of nitrogen balance measurements done on six children are shown in FIGURE 1. Examination of these diagrams reveals that patient G.S., maintained on a free-selection normal diet during a course of Corticotropin (Wilson) treatment, suffered a severe nitrogen loss during the first seven-day period on the hormone. This loss continued with decreasing severity throughout the treatment period. In the two weeks following therapy, the nitrogen retention exceeded the pre-treatment level—a compensatory effect usually noted after instances of excessive tissue breakdown.

In contrast, patient W.A., maintained on the synthetic diet throughout treatment, suffered only a negligible decrease in nitrogen retention in the face of a greater dosage of hormone than was given patient G.S.

Chromatographic analyses of the urine and blood specimens, collected during these studies of patients on free-selection diets, disclosed that, during periods of low or negative nitrogen retention, there occurred a marked elevation of the blood amino acids and an excessive loss of amino acids by way of the urine. These changes involved methionine, histidine, lysine, and

G.S., Male, 7.5 yrs., 22.8 kg., N intake, 390--440 mg./kg./day



W.A., Male, 7.0 yrs., 25.3 kg., N intake, 400--500 mg./kg./day

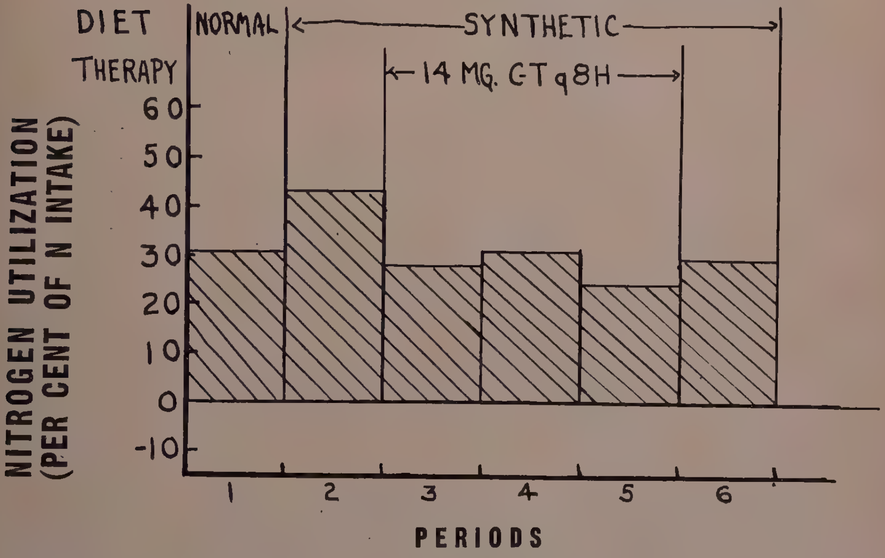


Figure 1. The effect of Corticotropin and diet on the nitrogen retention of children with rheumatic heart disease. Each study period comprised seven days.

threonine, in particular.[6] This occurred slightly, or not at all, in patients maintained on the synthetic diet. These findings, although preliminary, suggest that supplementation of the diet with these specific amino acids or equivalent amounts of protein from animal sources might prove beneficial during hormonal therapy.

From these experiences, it appears that the increase in appetite, which has been observed by many investigators to accompany hormonal therapy, is not always sufficient to cover the nutrient losses which are induced by these medications. It is not our purpose to suggest that special diets, such as we have constructed, be fed routinely to all patients receiving ACTH or cortisone. It is our intent, however, to recommend, on the basis of these continuing studies, that during periods of such therapy the diet of patients be generously supplemented, not only with proteins, but also with fats and carbohydrates in concentrated forms.

The practical and public-health implications of these nutritional aspects of ACTH or cortisone therapy are increasing daily. Currently, five to eight million people in this country are being treated with these drugs. The need for proper nutritional management of such patients and for more comprehensive studies in this field is obvious.

Protein-Sparing Action of Carbohydrates. Following the afore-mentioned experiences, studies were undertaken to increase the nutritional value of our synthetic diet. This we attempted to do by changes in the carbohydrate fraction.[7] This approach was suggested by indirect evidence, presented by a number of investigators, which indicated that fructose exerts a greater protein-sparing action than glucose in experimental animals.[8]

In order to obtain an objective evaluation of the relative protein-sparing activity of various sugars, the effect of the diets shown in TABLE 2 on the nitrogen retention of four normally growing children was measured. These diets, which supplied normal amounts of protein daily, were purposely made low in protein calories, and high in carbohydrate calories. This was done to accentuate any possible protein-sparing effect. The amount of fat emulsion was not changed. To achieve optimal and uniform absorption of these diets,

TABLE 2

COMPOSITION OF DIETS*

Constituents	*Calories, %*
Milk proteins (mixtures of whole milk and Sheffield milk protein)	10
Oral fat emulsion (Upjohn)	35
Carbohydrates (mixtures of lactose, dextrose, fructose, and sucrose)	55
Total	100
Vitamin supplements:	
Vitamin C, ml. orange juice/day	100
Vitamins A and D, ml. cod liver oil/day	15
Fluid supplement:	
Fruit juices and water, ml. fluid/cal.	1

* All diets supplied 1.3–3.0 grams of protein per kg. of body weight per day.

TABLE 3

EFFECT OF CARBOHYDRATE DISTRIBUTION ON NITROGEN RETENTION OF CHILDREN*

Subject Sex Age, yr.	Weight Initial, kg. Final, kg.	Nitrogen intake, mg./kg./day	Diet Period	Carbohydrate Distribution			Urinary fructose, mg./day	Blood sugars, mg./100 ml.		Nitrogen retention, mg./kg./day
				Fructose, %	Dextrose, %	Galactose, %		Total	Fructose	
J.C.	33.2	334	1	4.6	52.3	43.0	64	117	—	68.4
M	35.0		2	4.6	85.6	9.6	131	122	0	69.0
9			3	71.0	19.0	9.6	245	127	11	98.0
			4	39.0	53.0	9.6	121	137	4	67.0
R.S.	26.0	398	1	5.0	84.0	11.0	117	100	0	112.0
M	26.8		2	69.0	20.0	11.0	368	132	9	132.8
7			3	37.0	52.0	11.0	156	124	3	120.0
J.W.	47.0	205	1	37.6	52.3	10.2	388	130	4	29.4
F	47.9		2	4.9	84.9	10.2	230	143	1	24.6
12			3	70.1	19.7	10.2	575	132	5	51.2
G.Y.	38.0	294	1	37.8	52.4	9.8	136	104	3	69.2
M	39.2		2	4.4	85.9	9.8	84	94	1	76.4
9½			3	71.2	19.0	9.8	210	109	3	115.2

* All results given as daily averages of seven-day diet periods.

they were prepared daily to constant fluidity, and fed at the usual mealtime intervals. The acceptance of the diets was very good.

Data on nitrogen retention were secured by subtracting from the daily nitrogen intake the total nitrogen output as found by micro-Kjeldahl analyses of the excreta. The children were weighed daily during the course of the study.

The results of this study are summarized in TABLE 3. It is clear from the nitrogen retention values that diets containing approximately 70 per cent of the total carbohydrate as fructose induced a marked increase in nitrogen retention in all the children tested. In as much as this result was not obtained with diets high in galactose or dextrose, it seems reasonable to assume that the effect achieved with the high-fructose diet is in some way associated with the increased utilization of this hexose. In other tests, it was found that an isocaloric reduction of the daily protein-nitrogen intake, from a normal value of 300 mg. per kilogram of body weight to 200 mg. per kilogram of body weight, diminished or voided the exceptional protein-sparing effect of the high-fructose diets.

It is apparent from these results that, perhaps, the protein catabolic effects of hormonal therapy might be more effectively offset by high-fructose diets than with other diets. This possibility remains to be tested.

Oral Dietary Supplements in Convalescence. Prior to the advent of oral fat emulsion, we had employed a variety of milk-protein supplements on some 150 convalescents. These supplements consisted of 30–50 grams of protein product suspended in 500 ml. milk which was given in three portions at mid-meal intervals. Little or no interference with normal meal-time appetite was noted on a balanced hospital dietary which provides 2200–2400 calories per day. The patients ranged in age from 5 to 86 years and were in the nonacute recovery phase of various diseases or surgical procedures. In terms of body-weight gains and clinical signs, the older patients of this group showed a better response to the protein supplements than those under 40; and all fared somewhat better than a comparable control group which did not receive protein supplements.[9]

In the course of these studies, we were acutely aware of the fact that an appreciable portion of the protein supplement was utilized as source of energy rather than as a source of amino acids for the rebuilding of wasted muscle tissue and body proteins. Consequently, when oral fat emulsion became available, we began adding it to our dietary supplements in varying amounts. To date, we have tested this product as an additive to the protein-milk mixtures in some 30 patients. Some of our results are shown in TABLE 4. In general, the acceptance of the oral fat emulsion containing supplements has been good. In some instances, acceptability could be improved by flavoring with vanilla or chocolate. The effect on body weight and clinical condition of the patients has also been good, or, in some cases, better than the average results obtained with the protein supplements alone. These studies are being continued in order to secure statistical significant data.

Intravenous Feedings with Oral Fat Supplementation. In a previous pub-

TABLE 4

EFFECTS OF ORAL FAT EMULSION CONTAINING DIETARY SUPPLEMENTS IN UNDERWEIGHT ADULT CONVALESCENTS

Patient	*Sex*	*Age, yr.*	*Initial wt.*		*Diagnosis*	*Caloric Composition of Supplement*				*Days of supplement*	*Weight change*	*Acceptance of supplement*
			lb.	*%* *		*Milk*	*Protein*	*OFE*†	*Tot.*			
C.J.	M.	33	130	72	Malnutrition Pneumothorax Nervous tension	280	200	200	680	30	+6	Fair
C.L.	F.	45	118	78	Arthritis Malnutrition fr. prolonged Cortisone therapy (6 mos.)	280	200	400	880	5	+3.5	Good
P.C.	M.	79	88	62	Arteriosclerosis Malnutrition	350	200	100	650	14	+4	Fair
Q.M.	F.	71	118	85	A.S.H.D.	280	100	200	580	28	+8	Good
O'D.B.	M.	63	131	73	Malnutrition following pneumonia—Friedlanders	280	200	200	680	40	+16	Good
B.J.	F.	77	98	74	Rectosigmoid Ca.	280	200	400	880	12	+8	Good

* Body weight given as percent of standard derived from Metropolitan Life Insurance Co. Age–Height–Weight Tables, 1951 revision.

† Oral fat emulsion, Upjohn.

TABLE 5

NITROGEN BALANCE OF PATIENTS MAINTAINED COMPLETELY ON INTRAVENOUS SOLUTIONS WITH ORAL FAT EMULSION SUPPLEMENTS*
(TOTAL DAILY CALORIC INTAKE, 2400 CALORIES)

Periods	*A*	*B*	*C*
5% Bovine plasma hydrolysate	2 liters/day (16 g. N; 400 cal.)	—	—
5% Bovine plasma hydrolysate with 5% dextrose	—	2 liters/day (16 g. N; 800 cal.)	—
5% Bovine plasma hydrolysate with 5% dextrose and 7.5% ethanol	—	—	2 liters/day (16 g. N; 1850 cal.)
Oral Fat Emulsion (4 cal./ml.)	500 ml.; 2000 cal.	400 ml.; 1600 cal.	140 ml.; 560 cal.
C.H. male, 63 yrs., 150 lbs. Cerebral arteriosclerosis with marked dysphagia	+ 3.35	+ 2.36	+ 4.89
P.B. female, 64 yrs., 100 lbs. Bronchopneumonia, generalized arteriosclerosis	+ 3.69	+ 0.67†	+ 2.59
P.E. female, 77 yrs., 136 lbs. Duodenal ulcer, generalized arteriosclerosis	+ 0.80†	+ 1.70	+ 5.98
J.J. male, 61 yrs., 190 lbs. H.C.V.D. and A.S.H.D., pneumonia, right hemiplegia	— 5.56	— 5.56	— 5.12

* All intravenous solutions kindly supplied by Dr. Daniel R. Borgen of the Baxter Laboratories.

Oral fat emulsion (No. R9268) kindly supplied by Dr. Earl L. Burbidge of the Upjohn Company.

† Fat emulsion given 1 hour after infusions.

lication,[10] we reported that the output of nitrogenous metabolites, following the intravenous infusions of five per cent bovine plasma digest alone or with five per cent dextrose, indicated that the infused amino acids were relatively well utilized and that, in some instances, utilization was improved by the presence of five per cent dextrose. Subsequently, we attempted to improve the availability of the infused amino acids by increasing the total daily caloric intake. This was achieved by the addition of ethanol to the protein digest and dextrose solutions, and by the oral administration of fat emulsion. These solutions (five per cent bovine plasma digest, five per cent bovine plasma digest with five per cent dextrose, and five per cent bovine plasma digest with five per cent dextrose and 7.5 per cent ethanol, supplemented isocalorically to 2400 calories daily with oral fat emulsion) were tested serially in 16 patients recovering from a variety of ailments or surgical procedures. These patients received no other foods during the test period. Typical results are shown in TABLE 5. It will be noted therein that good nitrogen balances were observed in all instances but one. This single exception in our series is shown only to demonstrate that such refractory cases do occur, and that they do not vitiate in any sense the value of the benefits commonly derived from intravenous alimentation.

It is clear from these data and our previous report[10] that greater utilization of the infused nitrogen is achieved when an effort is made to increase the caloric intake of the patient. Attention is called to the fact that the highest nitrogen balances were obtained with the preparations containing alcohol. This is believed to be partly due to the sedation produced by this ingredient. The need for administering the oral fat supplement within the period of the infusion is clearly indicated by the chance finding that low nitrogen balances resulted when administration of this supplement was delayed one hour or more. These studies will be reported in greater detail elsewhere.[11]

Summary

It is apparent from the foregoing that, in order to achieve their maximum effect, therapeutic nutritional measures must fully recognize and apply the nutritionally important biochemical mechanisms such as the protein-sparing action of carbohydrates, the calorie-sparing value of fats, and the essential, amino acid-sparing action of nonessential amino acids. The commercial availability of fat emulsion will greatly facilitate the preparation of therapeutic diets of optimal biological value. In our experience, such diets or supplements can be prepared with high acceptance and nutritional value. This was found to be true not only in oral nutrition but also in parenteral nutrition.

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THE USE OF ORAL FAT EMULSIONS IN EXPERIMENTAL AND CLINICAL MEDICINE

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Emulsions of the generally available vegetable fats (olive, peanut, coconut, and pecan oils), with the addition of carbohydrate (sucrose or glucose), and, in some cases, of vitamins, the essential minerals, and protein, have proven useful in several experimental studies, as well as in the practical management of certain patients. The purpose of the present paper is to describe our procedures and experiences in the use of such preparations.

I. Use in Experimental Studies

Our use of oral fat emulsions was first directed to the problem of maintaining nephrectomized animals (dogs and rats) for prolonged periods.[1] The survival period following nephrectomy has been shown[2] to be prolonged by the use of a salt-free diet, which avoids overload of the circulation, with its resultant pulmonary edema, and the deleterious effects resulting from the accumulation of potassium and other nonexcretable substances. Starvation, resulting as it does in an increased rate of endogenous catabolism, results in shorter periods of survival than when a normal diet is given.[2] The longest survival periods are noted with the administration of an adequate caloric intake, consisting of fat and carbohydrate, and free of protein and salts. For such a purpose, emulsions of fat in aqueous carbohydrate solutions have proven to be entirely satisfactory. Such emulsions, prepared as described below, are eaten voluntarily by some animals for the period immediately following nephrectomy. Subsequently, however, they develop anorexia, and the mixture must be force-fed through a stomach tube in order to permit an adequate caloric intake, and the maintenance of the endogenous protein catabolism at a minimum.

Although the above described simple mixture is adequate for acute experiments extending over the short average period of survival of the nephrectomized rat (4.6 days) or dog (6 days), a more complete diet is necessary to prevent malnutrition in animals maintained for prolonged periods by the use of the artificial kidney[3] or peritoneal lavage.[1] The composition of such a diet is shown in TABLE 1. This diet contains the necessary vitamins and

TABLE 1

COMPOSITION OF SYNTHETIC DIET USED FOR THE MAINTENANCE OF THE BILATERALLY NEPHRECTOMIZED DOG

Peanut oil	420 ml.	Liver concentrate	1 g.
Lactalbumin	200 g.	Vitamin mixture	5 ml.
Glucose	500 g.	Acacia	30 g.
Ferrous sulfate	2 g.	Polysorbate 80	100 ml.
Water to make	2600 ml.		

minerals, and a requisite amount of a complete protein (lactalbumin). The polysorbate and acacia are added to stabilize the emulsion, which is formed by passing the mixture through a mechanical homogenizer. The polysorbate also probably aids in the absorption of the fat. The composition of the vitamin mixture is reported elsewhere.[1]

The diet mixture of TABLE 1 has a caloric value of 2.23 calories per ml. Accordingly, in order to supply the dog with its normal caloric requirement of 70 calories per kilogram of body weight, 31 ml. of the diet mixture per kilogram of body weight is administered daily, divided in two or more doses. In addition, the animal is allowed free access to water. The diet of TABLE 1 has served satisfactorily in maintaining nephrectomized and nephrectomized adrenalectomized dogs for periods of 30 to 70 days in an apparently good state of nutrition. The appearance of one of the dogs, which was sacrificed on the 70th day following nephrectomy, is shown in FIGURE 1, as it appeared two months following operation. The relatively good state of its nutrition is apparent. During the latter period of their life, the animals did manifest some loss of weight, varying from 7 per cent of its original weight in an animal sacrificed on the 38th day, to 32 per cent in another sacrificed on the 70th day following bilateral nephrectomy.[1] However, in view of the malignant hypertension which the nephrectomized animal manifests,[4] this observed loss of weight is to be anticipated.

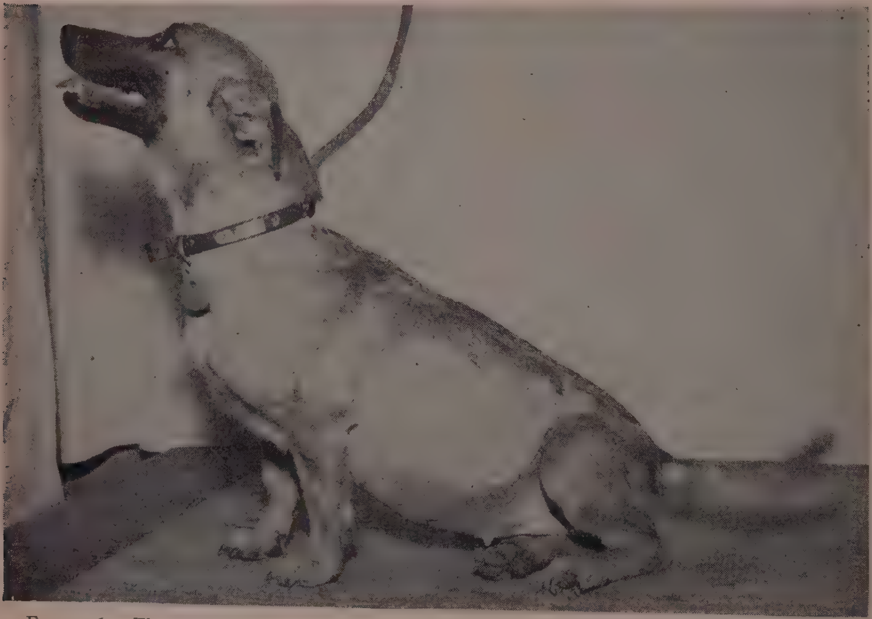

FIGURE 1. The appearance of a dog 60 days following bilateral nephrectomy, and maintained during this period on the diet of TABLE 1.

Intermittent peritoneal lavage, which was used in the above-mentioned experiments, affords a procedure for investigating various problems involving balance studies. The possibility of using a synthetic mixture of known composition, such as the diet of TABLE 1, adds to the practicality of such studies.

II. Clinical Applications

Our clinical use of oral fat emulsions has been directed toward several diverse conditions. The clinical counterpart of the experimental studies on nephrectomized animals is encountered in patients with acute renal failure. Such patients must also be maintained during the period of oliguria or anuria on a protein-free, electrolyte-free diet of sufficient caloric value to reduce the endogenous protein catabolism to a minimum.[5] Borst,[6] of Holland, in 1948, first suggested such diets, which were composed principally of sugar and butter. Their unpalatability to British patients led Bull, Joekes, and Lowe[7] to devise a simple emulsion, containing glucose (400 grams) and peanut oil (100 grams) in water (sufficient to make 1 liter), and emulsified by the addition of acacia. This diet was administered by drip through a plastic tube (2 to 3 mm. in diameter) passed through the nose into the stomach. One liter of the above-described mixture furnished 2500 calories daily, and also sufficient water to equal the volume of insensible perspiration. We have utilized emulsions similar to those of Bull, Joekes, and Lowe, those prepared with the more palatable coconut oil, and those now available commercially. If necessary, the emulsions were administered by nasal tube, but, in most cases, they were tolerated when given orally in doses of 15 to 30 ml. every one-half to one hour during the patient's waking hours. When used in the latter way, the mixture is flavored with a suitable agent (fruit syrup, chocolate, or vanilla extract) in order to render it more palatable. The emulsions are tolerated well by most patients, but, in some, anorexia makes oral ingestion impossible.

The intravenous administration of 10 or 15 per cent glucose or invert sugar has been considered adequate for the needs of most patients suffering from reversible renal failure. Higher-caloric diets, made possible by the administration of oral fat emulsions, are, however, obviously more effective and lead, as demonstrated by Bull, Joekes, and Lowe, to reducing the rate of rise of the blood-urea level to a minimum. The higher caloric content of fat emulsions is particularly desirable in patients in whom infectious, traumatic, or other complications increase the rate of endogenous protein catabolism.

Oral fat emulsions may be used with advantage not only in patients with reversible acute renal failure, but also in other conditions (e.g., in acute exacerbation of chronic pyelonephritis, in malignant hypertension, *etc.*) where an elevation in blood urea levels makes it desirable to reduce endogenous protein catabolism to a minimum. We have also used oral fat emulsions in patients in whom anorexia or dysphagia made it desirable to supplement their normal diet with a high-caloric, easily consumed liquid concentrate, such as is offered by carbohydrate-fat emulsions. For this purpose, the diet of TABLE 1 has been used as a supplement, given between the regular meals. Although not relished, it has been possible to administer it if it is properly flavored as already described, and given in frequent small doses. The diet has also been used in this way in normal individuals in whom a gain in weight was desired.

For the purposes just outlined, the commercially available preparation (Lipomul-Oral) has proven satisfactory. This mixture contains four calories per cubic centimeter. The unpalatability of such mixtures is the chief drawback to their use but the addition of flavoring agents has increased their acceptability, particularly when administered diluted with milk.

Summary

Emulsions of fats in the form of vegetable oils in aqueous solutions of sugars, and modified by the addition, when circumstances demanded it, of vitamins, proteins, *etc.* have been found to be useful dietary adjuncts in certain experimental studies as well as in several clinical conditions.

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THE USE OF ORAL FAT EMULSIONS IN SURGICAL PATIENTS BY MOUTH, GASTROSTOMY, AND JEJUNOSTOMY—CLINICAL AND METABOLIC STUDIES

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Many surgical patients with obstructing lesions of the mouth, esophagus, and stomach can consume only a liquid diet. These patients often enter a charity hospital weeks or months after the onset of symptoms. As a result, severe malnutrition is usually present, which greatly intensifies the risk of performing an extensive surgical procedure, such as esophagectomy or total gastrectomy. In the past, the restoration or maintenance of body weight, positive nitrogen balance, and an adequate caloric, mineral, and vitamin intake, while restricted to a liquid diet, has been achieved only with difficulty. Recent work[1-4] has indicated that fat emulsions can be used as the major source of calories in a liquid diet. This study was undertaken to determine whether a high-caloric liquid feeding could be administered to such patients as a supplemental or complete feeding, and whether this would be accompanied by weight gain, restoration of positive nitrogen balance, and minimal alteration in normal metabolism.

Experimental Procedures and Methods

Seventy-six patients, requiring prolonged liquid feeding for obstructive lesions of the mouth, esophagus, or stomach, were selected for the study. All of these patients had had some degree of weight loss preceding the study. All patients received a high-caloric liquid feeding, consisting primarily of a 40 per cent emulsion of peanut oil.* This emulsion supplies 4.0 cal. per ml. The feedings were either supplemental to a ward liquid diet, or they consisted of a complete diet of fat emulsion in combination with a protein concentrate.† The supplemental feedings were administered between meals, and before bedtime. Complete feedings were made up to include the daily requirements of electrolytes, minerals, and vitamins, and were administered slowly throughout the day. These feedings were prepared by adding 100 grams of the protein concentrate, which also contained many vitamins and minerals, to 1000 ml. of the fat emulsion. One hundred mg. of ascorbic acid, 4.0 grams of sodium chloride, and 85 mg. of iron were added to assure

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* Lipomul, Oral (Upjohn), a 40 per cent emulsion of peanut oil, with 10 per cent dextrose, 2 per cent purified soybean phosphatide and 0.2 per cent synthetic emulsifier (alkylarylpolyether alcohol). One thousand ml. of this emulsion contains 200 mg. sodium, 250 mg. potassium, 140 mg. chloride, 50 mg. calcium, and 600 mg. phosphorus.

† Somagen (Upjohn), 100 g. contains 70 g. milk protein, 22 g. dextrose, 150 mg. sodium, 1.40 g. potassium, 1.20 g. chloride, 1.40 g. calcium, 1.0 g. phosphorus, 5 mg. thiamine, 5 mg. riboflavin, 2 mg. pyridoxine, 10 mg. calcium pantothenate, 30 mg. nicotinamide, 2 mg. folic acid, 2 g. liver concentrate, and yeast extract from 15 g. yeast.

Lipomul and Somagen were generously supplied by E. L. Burbidge, M.D., Upjohn Company, Kalamazoo, Michigan.

minimal supply of all vitamin and mineral requirements. Whenever fat emulsion was given without a ward diet, the above supplementation was added.

The patients were divided into three groups. Group I consisted of 51 patients with incomplete obstructive lesions, who were administered the feeding by mouth. When the fat emulsion was used for supplemental feeding, it was administered in varying doses. All of the early patients were started on 90 ml. per day, and the dosage increased by 90 ml. per day. Later, the initial dosage and daily increase was changed to 180 ml. per day. The last patients were started on dosages ranging from 450 to 1080 ml. per day. Whenever a patient was unable to tolerate the emulsion, flavoring agents were added. If the intolerance continued, the dosage was reduced or discontinued, and then restored.

Group II consisted of 20 patients with complete obstructive lesions, who were fed the fat emulsion by gastrostomy or jejunostomy. These patients received between 300 and 1000 ml. of the fat emulsion either as a supplement to the ward enteric diet, or as a complete feeding. In order to use the complete feeding entericly, the fluid content was varied to meet individual requirements. Whenever diarrhea developed, the volume of fluids was reduced, and bismuth subcarbonate and potassium chloride were added, if indicated.

Group III consisted of five patients with wired jaw due to fracture of the mandible, who could consume only liquids. Special metabolic studies were carried out on this group. All these patients received 1000 ml. of the fat emulsion daily, supplemented by protein, minerals, and vitamins, as described above.

All patients were weighed at frequent intervals whenever possible, and control weights were recorded for a period preceding and following the feedings. Each patient reported all subjective changes in bowel habits, appetite, digestive symptoms, and strength. In Group III, the following determinations were made: urine volume and nitrogen excretion, daily; urinary ketones, semi-weekly; fecal nitrogen and fat excretion, 3–5-day collections; blood fat, phospholipid, CO_2 content, NPN, FBS, weekly; serum total protein and A/G ratio, free and total cholesterol, sodium, potassium, and chloride, weekly; BMR and RQ, weekly.

Results

Group I. The results on 41 patients who received the fat emulsion by mouth are summarized in TABLE 1. The average daily dose varied from 300 to 1080 ml. and averaged 762 ml. for all 41 patients. Thirty-three, or 80.5 per cent of the patients gained weight, with an average of 5.5 pounds in an average of 11.7 days. The weight gain ranged from 1.5 to 17 pounds over a period of from 5 to 25 days. The average daily weight gain per 734 ml. of the fat emulsion was 0.47 pounds. Sixteen patients, or 39 per cent noted an increase in appetite, and 26, or 63.4 per cent noted a feeling of increased strength. Eighteen, or 44 per cent noted no disagreeable symp-

TABLE 1

	Patients		*Av. total daily intake*				*Av. emulsion suppl.*						
	No.	*Av. age*	*Carbohydrate, g.*	*Protein, g.*	*Fat, g.*	*Cal.*	*Days, no.*	*Daily intake, ml.*	*Daily cal.*	*Weight gain, no.*	*Av. weight gain, lb.*	*Weight loss, no.*	*Av. weight loss, lb.*
Group I													
Oral	41	55	199	76	337	4133	13.5	762	3048	33	5.5	8	5.0
Group II													
Enteral													
gastrostomy	9	59	193	69	333	4045	22.0	676	2704	5	10.2	4	3.2
jejunostomy	11	62	154	70	251	3135	12.0	609	2436	3	8.0	6	6.3
Group III													
Oral	5	36	122	70	400	4368	18.8	1000	4000	5	7.6	0	0.0

toms of any sort. Eighty per cent of the patients were able to tolerate the emulsion, and to continue the prolonged feedings.

Eight patients, or 19.5 per cent failed to gain weight. Ten other patients (not included in the table) were started on the fat emulsion but, because of disagreeable symptoms, the feedings were discontinued during the first few days. Of the total of 51 patients administered the fat emulsion by mouth, 14, or 27.4 per cent refused further feedings after developing nausea, vomiting, diarrhea, or constipation. Six of these patients developed nausea or vomiting with the first dose of the fat emulsion; two refused further feedings after their second episode of nausea and vomiting in the course of the first three days of feeding; and one refused further feedings after developing a mild constipation on the fifth day. A total of twenty-four, or 47 per cent of the patients developed varying degrees of nausea and vomiting.

Of the patients on prolonged administration of the fat emulsion, eight, or 19.5 per cent developed constipation, five or 12 per cent developed a mild diarrhea, and seven or 17 per cent noted a decreased appetite. It became necessary to discontinue treatment in only four of the prolonged feedings because of intolerance. Although the incidence of intolerance was high, in most cases it was of a rather mild nature.

Only two patients with nausea and vomiting gave a history of fatty-food intolerance. None of these patients revealed any observable gallbladder pathology on cholecystogram. There was no particular correlation between the original dosage and the development of disagreeable symptoms.

Group II. The results obtained with the 20 patients in Group II on gastrostomy and jejunostomy feedings are summarized in TABLE 1. This group included nine patients with a gastrostomy, and eleven patients with a jejunostomy. The average amount of fat emulsion administered per day ranged from 250 to 1000 ml., and averaged 627 ml. for all twenty patients. Eight patients, or 40 per cent gained weight. The weight gain ranged from 3 to 22 pounds over a period of from 5 to 49 days. The patients gained an average of 9.4 pounds in an average of 26.6 days. The average daily weight gain per 685 ml. of the fat emulsion was 0.35 pounds. Five of the patients noted an increase in appetite and eight noted an increase in strength. Eight patients experienced no disagreeable symptoms of any sort during the feedings. Ten patients failed to gain weight. The weights on two patients were unrecorded because they could not be weighed. Eleven patients with far advanced carcinoma expired because of their illness during the feedings. Nine of the ten patients who failed to gain weight belonged to this group with far advanced carcinoma. Three of the patients who failed to gain weight over the entire period recorded weight gains in the first four to seven days of feeding.

Eleven patients had diarrhea, two patients developed nausea and vomiting, and one patient was constipated. In the patients with a jejunostomy, a slow drip, over a 12–16 hour period, was most effective in controlling diarrhea.

Hasty administration was always accompanied by disagreeable symptoms of diarrhea and occasionally nausea and vomiting.

Group III. The results obtained with the five patients in Group III on oral feedings and metabolic balance studies are summarized in TABLE 1 and FIGURES 1 and 2. All patients gained weight on the fixed intake of 1000 ml. of fat emulsion in a complete feeding. The weight gain ranged from 2.75 to 12.25 pounds in a period of 12 to 24 days, or an average of 7.6 pounds in an average of 18.8 days. The average daily weight gain per 1000 ml. of fat emulsion was 0.4 pounds. All patients noted an increase in strength, and four noted an increase in appetite. Two patients developed symptoms of intolerance and were not suitable for metabolic studies; their results are included in Group I.

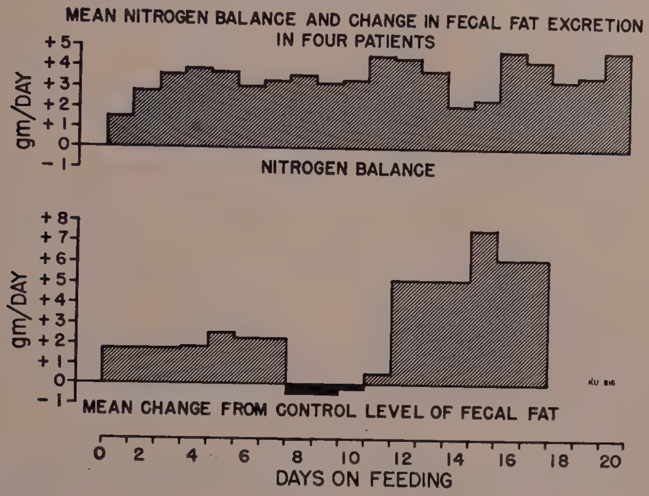

FIGURE 1.

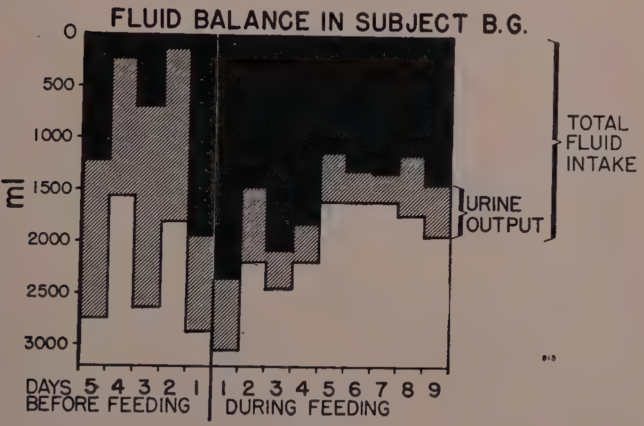

FIGURE 2.

While on a fixed intake of 400 grams of fat per day, the mean daily fecal excretion of fat increased above the control level by only 7.68 grams as a maximum, and averaged only about 3 grams a day. The daily fecal fat excretion ranged from 2.20 to 24.8 grams per day, or from 0.55 to 6.20 per cent of the amount ingested. These results are shown in FIGURE 1. The weekly fasting blood studies revealed no increase in total fat, neutral fat, phospholipid, or cholesterol. Urinary ketones were only occasionally detectable in trace amounts, and disappeared with increased fluid intake.

The results of the nitrogen balance studies are also shown in FIGURE 1. All the patients were maintained in positive nitrogen balance on a fixed intake of 70 grams of protein daily, with an average positive balance of 3.46 grams of nitrogen per day. The mean daily nitrogen retention ranged from 1.39 to 5.04 grams. There was no consistent change in serum total protein, A/G ratio, N.P.N., fasting blood sugar, CO_2, sodium, potassium, or chloride. All determinations of urine urobilinogen excretion remained within normal limits.

All of the BMR determinations remained within normal limits, but apparently increased slightly within these limits during the course of the feeding. The respiratory quotient decreased from the control value, or remained low in all patients. Most of the values obtained while the feedings were in progress ranged between 0.71 and 0.79.

Because it was noted in two patients that urine volume decreased while the feeding was in progress, fluid balance was studied in one patient. These results are shown in FIGURE 2. This study revealed that, although there was a slight decrease in total daily fluid intake, the daily urine output was depressed markedly.

Discussion

Theoretically, a high-caloric diet is desirable for a patient suffering from malnutrition. Rubner,[5] Newman,[6] Jansen,[3] and Zuntz[8] have shown that, without change in daily protein intake, nitrogen balance can be converted from negative to positive merely by caloric supplementation. With carbohydrate or protein as the major source of calories, high-caloric supplementation in liquid form has not been practicable. Fat has the advantage of a higher caloric density, but, in the past, a suitable method of administration was not available. Stare and his group[1] have demonstrated that orally administered fat emulsions are relatively well tolerated. The previous work in the field has included few surgical patients, and, in general, the total daily caloric intake, although adequate, has not been at the high levels achieved in our study. In addition, the previous studies have utilized fat emulsions primarily as a supplemental feeding. In this study, the emulsion was used as the major source of calories. Carbohydrate, protein, minerals, and vitamins were added merely to supply theoretical daily minimal requirements. The majority of patients received no food other than fat emulsion to which was added protein concentrate, minerals, and vitamins. This preparation actually consisted of a complete feeding of very high-caloric value which could be administered by mouth, gastrostomy, or jejunostomy. Many of the patients received between 4000 and 5000 calories per day, some actually received more than 5000 calories daily.

A question arises concerning the value of high caloric alimentation of this type. A striking clinical response was noted in patients with benign obstructive disease of the upper gastrointestinal tract. These patients rapidly gained weight and strength. Several patients who appeared pre-terminal showed dramatic improvement following high-caloric therapy. A similarly excellent response was noted in patients with malignancy of the mouth. A variable response was noted in malignancy of the esophagus and stomach, depending upon the stage of the disease. In general, preoperative feedings in patients with resectable lesions gave good results, whereas those patients with far-advanced lesions showed only temporary, if any, benefit.

Fat-emulsion feedings can be administered with little difficulty by gastrostomy or jejunostomy, making available a much higher daily caloric intake than was previously possible. Although the gastrostomy feedings can be given rapidly, the jejunostomy feedings, as with other preparations, should be administered slowly.

The metabolic studies further demonstrate the value of high-fat alimentation. In spite of the fact that these patients received 400 grams of fat per day, the fecal fat excretion increased by an average of only about three grams daily. Previous studies have shown little change in fecal fat on diets containing 100–200 grams of fat per day,[9–11] but there are, however, only a few studies on diets containing over 300 grams of fat per day.[12] In addition, a marked positive nitrogen balance was present in these patients, as demonstrated by an average retention of 3.45 grams of nitrogen per day.

Another interesting feature of the metabolic studies was a decrease in in urinary volume. The exact significance of this is not understood as yet. We are, therefore, investigating the relationship of this decrease to urinary potassium and potassium balance. Theoretically, this decrease in urinary output may be harmful if it occurs in patients with renal or cardiac disease.

At present, patient intolerance to large doses of fat emulsion (due either to unpleasant taste or symptoms such as nausea, vomiting, diarrhea, or constipation) is the major difficulty in the use of this material. Although the majority of patients have continued therapy in spite of some mild symptoms, a few patients refused further therapy.

A final question arises concerning possible detrimental sequels following prolonged high-fat administration. There were no harmful effects noted in either the clinical or metabolic study. In addition, postmortem examination of several patients with far-advanced malignant disease revealed no demonstrable harmful effect from the prolonged daily administration of 400 grams of fat.

Summary and Conclusions

(1) A high-caloric feeding, consisting primarily of a 40 per cent fat emulsion, was administered to 76 patients.

(2) Administration of 400 grams of fat per day in the upper gastrointestinal tract is usually tolerated, and is almost completely absorbed.

(3) A marked increase in weight occurred in patients with benign obstructing disease of the upper gastrointestinal tract and in malignancy of the mouth. Beneficial results were also noted in some patients with malignant obstructing lesions of the upper gastrointestinal tract. Little, if any, improvement occurred in patients with far advanced malignant disease.

(4) Marked positive nitrogen balance can occur with moderate-protein high-caloric intake.

(5) Nausea, vomiting, diarrhea, or constipation occurred in approximately 50 per cent of our cases. The symptoms were often mild and transitory and usually did not require cessation of the therapy.

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THE USE OF AN ORAL FAT EMULSION IN THE SUPPORTIVE TREATMENT OF PULMONARY TUBERCULOSIS

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In few chronic diseases are the nutritional aspects of medical treatment more important than in pulmonary tuberculosis. This aspect is significant, whether viewed from the preventive or the therapeutic standpoint.

Downes[1] has reported that the incidence of pulmonary tuberculosis over a five-year period was lower in a group of Negroes receiving dietary supplements than in a group of similar control subjects. When manifest disease is present, toxemia and fever combine to increase tissue breakdown, with resultant loss of nitrogen and decrease in body weight. The operative procedures used, and the gastrointestinal disturbances and anorexia characteristic of the disease further contribute to this tendency. Certain drugs, such as para-aminosalicylic acid, which are used in the treatment of pulmonary tuberculosis, may also cause anorexia and nausea, and contribute to the loss of body weight. Manifestations of various vitamin deficiencies are not uncommon among patients with active pulmonary tuberculosis.[2, 3]

The present study was undertaken to discover whether a dietary supplement of small volume but high caloric content would be of value in the supportive treatment of patients with pulmonary tuberculosis. The results, obtained with the use of an orally administered fat emulsion in regard to tolerance and effects on weight, are described in this report.

Sixty-three patients, with pulmonary tuberculosis of various degrees, were studied. The group consisted of 47 males and 16 females, ranging in age from 22 to 63 years. All of the patients were hospitalized in county institutions. Care was taken to exclude any patient who showed clinical evidence of tuberculosis enteritis, but no patient was omitted from the series because of current or contemplated treatment with artificial pneumothorax, pneumoperitoneum, para-aminosalicylic acid, or dihydrostreptomycin. As far as possible, selection was limited to cooperative and underweight patients without signs of significant recent alterations in the disease. No patient with a distinct intolerance of fats was included, although minor degrees of intolerance were present in approximately ten per cent of the group.

The fat emulsion used was a commercially prepared product, containing 40 per cent vegetable oil and ten per cent dextrose, with a value of four calories per milliliter.* Fifteen patients were offered two ounces of the emulsion twice daily, and once at bedtime. Forty-eight patients received a mixture of two ounces of fat emulsion in 170 ml. of milk, with added milk protein,† which furnished 411 calories, with 15.4 grams of protein. Of the 48 patients, 33 received one dose of the standard mixture once daily for 13 weeks, seven received one dose daily for briefer periods, while eight patients succeeded in taking two or three doses of the mixture daily for as long as 22 weeks (TABLE 1).

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* Lipomul-Oral, supplied by The Upjohn Co., Kalamazoo, Michigan.

† Referred to hereafter as the standard mixture.

TABLE 1

SEGREGATION OF PATIENTS

Emulsion only			15
Standard emulsion mixture*			48
Standard mixture once daily, 13 weeks		33	
Static disease	18		
Progressive disease	15		
Standard mixture 2–3 times daily, 1-22 weeks		8	
Standard mixture once daily, 3-7 weeks		7	
Total			63

* 2 oz. fat emulsion in 170 cc. milk, with added milk protein.

The emulsion or the standard mixture was presented as a medication and not as a food. The patients' weights were recorded weekly, and episodes of fever, pronounced alterations in the course of the disease, and side effects due to the emulsion were noted. The basic hospital diet contained 2,800-3,000 calories, including at least 150 grams of protein a day.

In the 15 patients who received a total of six ounces of unmixed fat emulsion daily, the period of toleration was so short that no evaluation of weight gains was possible. Because of anorexia or mild nausea, all 15 patients ceased accepting this amount of emulsion within ten days. Within the first week, two of the 15 patients experienced diarrhea, characterized by three to four soft, ill-formed, but not-bulky stools per day. After having taken six ounces of the emulsion daily for ten days, one patient was able to tolerate four ounces daily for an additional three weeks, one patient four ounces daily for another two weeks, and one patient one ounce daily for three weeks more. In these three patients, the emulsion was ultimately discontinued because of epigastric fullness, anorexia, or nausea. Before the emulsion was discontinued, the food intake of the 15 patients was significantly decreased. No greater weight gains were noted than might have been

TABLE 2

FREQUENCY OF OCCURRENCE OF VARIOUS SIDE EFFECTS DUE TO EMULSION AND STANDARD EMULSION MIXTURE*

Side effect	*Emulsion only, 6 oz. daily (15 patients)*		*Standard mixture, once daily (40 patients)*		*Standard mixture, twice daily (8 patients)*	
Epigastric fullness	15	(100%)	8†	(20%)	0	
Anorexia	12	(80%)	0		8†	(100%)
Nausea	3	(20%)	0		0	
Diarrhea	2	(13%)	3	(8%)	1	

* 2 oz. fat emulsion in 170 cc. milk, with added milk protein.

† intermittent.

expected without ingestion of the emulsion. In fact, two patients had lost two pounds at the end of three weeks.

In the 48 patients who received the standard mixture, toleration was generally satisfactory. Side effects due to the mixture were distinctly less than those caused by the emulsion alone (TABLE 2). Epigastric fullness was an intermittent complaint but, in no instance, was it necessary to discontinue the mixture for this reason.

Diarrhea, similar to that caused by the emulsion alone, occurred in four patients in this group. This symptom appeared in the second, third, sixth, and ninth week, respectively, in contrast to its early occurrence in patients taking the pure emulsion. The daily intake of emulsion in the latter group, however, was initially three times as great. It was not necessary to discontinue the emulsion because of diarrhea, and the symptom ceased spontaneously in one week in the three patients who were receiving one dose of the standard mixture daily. In the fourth patient, who attempted to take two doses of the standard mixture daily, diarrhea appeared after three weeks, but it ceased within one week when the intake was reduced to one dose daily.

A total of 33 patients took and tolerated the standard mixture for 13 weeks. The course of the disease remained stationary in 18 of these patients, and progressed in 15.

During this period, each of the 18 patients received 12 grams orally of para-aminosalicylic acid daily, and one gram of dihydrostreptomycin, injected intramuscularly, every third day. In all but three patients, a therapeutic pneumoperitoneum was maintained. In this group, the rate of weight gain seemed enhanced during the 13-week period, and two of the patients weighed more at the end of this time than they had during the previous two years in the hospital. The weight of one young woman increased from 100 to 113 pounds, despite the fact that she had several episodes of mild hemoptysis from bronchial ulcerations. The average weight gain for the group was 8.0 pounds, with a range of two to 15 pounds. In explanation of this modest gain in weight, it should be emphasized that, although the course of the disease was static in these patients, all of them had active tuberculosis, and many of them had transient episodes of fever during this time.

It appears that the addition of five pounds of body weight to an Oriental woman of 85 pounds is more noteworthy than a similar increase in a large-boned male weighing 170 pounds. Alterations in the body weights of the 18 patients were therefore, calculated as percentile changes from the weight just prior to the addition of the standard mixture. Expressed in this fashion, all patients gained from two to 12 per cent of their body weight in the 13-week period. In the 18 patients in whom the disease was static, the average rate of increase in body weight was greater during the time they were taking the emulsion than in the preceding control period (FIGURE 1). It is not clear why the rate of weight gain fell off after the ninth week.

In the 15 patients in whom the disease was progressive, prolonged periods of fever (102-103°F.) occurred, additional zones of the lungs became involved or cavitation increased, and, in one instance, renal tuberculosis became evident. Although the weight gains were meager (TABLE 3), it was our clinical impression that the loss of weight during the 13-week period was less than would ordinarily be anticipated in such patients. This opinion cannot be quantitated further, but it is supported by the fact that a greater loss of weight occurred in a group of control patients with progressive pulmonary tuberculosis, who did not receive the emulsion. In addition, although during periods of fever or toxicity patients sometimes failed to accept all of the food in their regular diet, all of them continued to take the standard mixture.

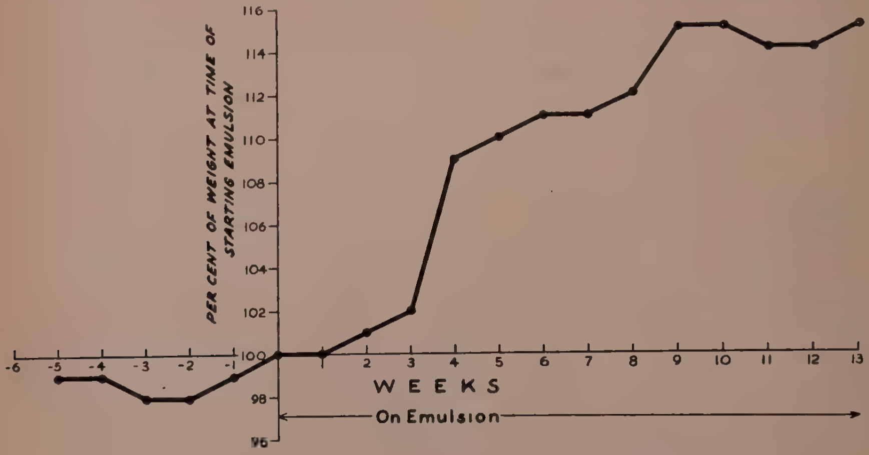

FIGURE 1. 18 cases pulmonary tuberculosis (no change in clinical status).

TABLE 3

WEIGHT CHANGES IN 15 PATIENTS WITH PROGRESS OF DISEASE

Lost 1-3 lb.	3	Gained 1-5 lb.	7
No change	4	Gained 5-10 lb.	1

Side effects of the standard mixture on the upper gastrointestinal tract were no more frequent in these patients than in the patients in whom the disease was stationary. Two of the three instances of diarrhea in patients receiving the standard mixture once daily, however, occurred in patients in whom the disease was progressive. It is possible that the diarrhea was due in part to unrecognized enteric tuberculosis, but this seems unlikely since the diarrhea was not prolonged.

To discover the maximum amount of the standard mixture which could be tolerated a day, eight patients were offered additional doses. The concentration of fat in the mixture was not altered. The patients took doses of the standard mixture two or three times a day. Two patients were able to ingest two doses of the mixture daily for seven weeks without ill effects, while five tolerated this amount daily for one week. In one patient who took three doses daily for 22 weeks, an increase in weight from 93 to 118 pounds occurred. Anorexia was an intermittent complaint in all patients, but was not severe enough to require discontinuation of the standard mixture.

In the remaining seven patients, administration of the standard mixture was interrupted by operation or by discharge from the hospital. These patients tolerated the standard mixture well, however, for periods varying from three to seven weeks. One of the patients requested the mixture three days after a thoracoplasty.

As judged by examination of stool specimens stained with Sudan III, the fecal excretion of fat was no greater in 12 patients receiving the standard mixture for 14 weeks than it was in control patients. This was true in two instances where diarrhea had been present previously.

Discussion

Prolonged toleration of undiluted fat emulsion is not likely in patients with active pulmonary tuberculosis. The frequent occult gastrointestinal complications of pulmonary tuberculosis may be one explanation. Steinbach[4] reported that intestinal tuberculosis was found in 65 per cent of patients with pulmonary tuberculosis who were examined at autopsy, and in approximately one-third of living patients who were examined by radiography of the gastrointestinal tract. He emphasized the fact that absence of gastrointestinal symptoms did not necessarily indicate absence of this complication.

When the fat emulsion is homogenized with milk and milk protein, tolerance is satisfactory. Considerable variation of tolerance, however, which apparently has no connection with the severity of the disease, is to be expected in individual patients. A few patients may accept as much as six ounces of the emulsion daily, when it is mixed with milk and milk protein. Ingestion of this amount of the emulsion will result in creditable gains in weight. Although much of the intolerance of the emulsion is doubtlessly due to the effect of fat on gastric motility and emptying, the addition of certain flavors might make the mixture more palatable. The emulsion was not distasteful to any patient, but it was found more acceptable when mixed fresh and presented cold. One of the most gratifying results of this study was the fact that even severely-ill patients tolerated the standard mixture exceedingly well.

The weight gain in our patients was perhaps less than might otherwise be expected, due to the fact that these patients were indigents who had entered the hospital from a poor social environment and were malnourished. In such patients, the change to bed rest and a generous hospital diet would be apt to cause an increase in weight. Thus, when the emulsion was added to the regimen several weeks after the patient was hospitalized, the rate of weight gain due to hospitalization *per se* tended to obscure that due to the emulsion.

The cause of the transient diarrhea experienced by several of the patients is not clear. It does not seem reasonable to attribute it to enteric tuberculosis. Further studies of the use of the emulsion in patients with other types of disease should shed light on this problem.

Summary

An oral fat emulsion was utilized as a dietary supplement in the supportive treatment of 63 patients with pulmonary tuberculosis.

The pure emulsion, even in amounts as small as two ounces daily, was not tolerated well, since it caused anorexia and nausea. When the emulsion was homogenized with milk and milk protein, it was tolerated in a satisfactory manner and for longer periods of time, even by patients in whom the disease was progressive. In patients in whom the disease was static, the rate of weight gain was increased by ingestion of the fat emulsion mixture, and the expected weight loss in patients with progressive pulmonary tuberculosis apparently was minimized.*

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EXPERIMENTAL STUDIES IN HUMAN GASTRIC PHYSIOLOGY—I. THE EFFECT OF FAT UPON GASTRIC EVACUATION AFTER PARTIAL GASTRECTOMY

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There are many patients in whom caloric supplementation is desirable. The high energy content of fat, as compared to other types of food, makes it especially suitable for such purposes. However great its theoretical advantages, in practice, it frequently has proved impossible to elevate the dietary fat intake to desired levels because of distressing symptoms or to frank intolerance caused by the fat. Beaumont's comment, that the "stomach is a creature of habit," is nowhere more true than in this situation. Individuals can be accustomed to increasingly high fat intake, but long periods of time are required, and such efforts are often only partially successful. The time element is sometimes important, as, for example, in the preparation of malnourished patients for surgery.

Many of the distressing side effects of ingestion of a high-fat diet are attributable to the delay in gastric emptying caused by the fat. The general features of this phenomenon have been known for a hundred years.[1, 2] but the exact mechanism of delayed gastric emptying after fat intake is not understood even today.

There is a generally held opinion that delayed gastric emptying after ingestion of fat is not related to the pyloric sphincter,[3, 4, 5, 6] but that it is rather due to gastric atony, and absence or diminution of peristalsis. Waugh concluded that closure of the pylorus is important,[7] but others thought that it is relaxed along with the remainder of the stomach.[8, 9, 10] Best and Taylor[3] state that "x-ray examinations of the stomachs of patients in whom the pylorus has been excised show emptying times which do not differ appreciably from the normal (Singleton)." Crider and Thomas[5] reported a personal communication from Dr. Singleton, advising that the above statement refers to unpublished observations made in "the examination of a number of cases who had Billroth I operations for duodenal ulcer, cases in which the pyloric sphincter and duodenal caput only were excised and end-to-end gastroduodenostomy performed. These cases obviously have no sphincter left in spite of which the emptying time of their stomachs was within normal limits." Crider and Thomas went on to say that "in the absence of opposing data it is reasonable to conclude that pyloric resection or other operations with similar functional significance do not shorten the total emptying time of the normal stomach of man or certain experimental animals." They held the pylorus of dogs open mechanically, and noted no shortening of gastric emptying with olive oil, glucose solutions, and hydrochloric acid solutions.

Waugh reviewed much of the literature on the effect of fats on gastric motility, and performed experiments which led to the conclusion that the "fat effect" followed contact of fat with the upper intestinal mucosa. This is in agreement with the results of Quigley, Zettleman, and Ivy.[11] McSweeney and Spurrell, however, concluded that normally the delayed emptying results from the direct action of the fat within the stomach, though they found a similar effect from fat in the duodenum.[12]

The mechanism of the gastric inhibition caused by fat was explained in part by Farrell and Ivy, who found inhibition of transplanted stomach pouches by fat introduced into the bowel. The latent period of the "fat effect" from the jejunum was five minutes.[13] They believed that the inhibition of gastric emptying was caused by some humoral agent. It has been shown that the inhibiting substance carried through the blood is not fat or chyle.[11, 14] Soaps, glycerine and fatty acids given intravenously have given variable results.[4, 11, 15]

In 1930, Kosaka and Liu found that extracts from the mucosa of bowel previously in contact with fats contained a substance, now known as "enterogastrone," which slowed gastric emptying and reduced gastric acidity.[16] Subsequently, it was found that it is not necessary to apply fat to the mucosa to get the enterogastrone. It is thought that delayed gastric emptying after ingestion of fat may result from the influence of such an agent upon the stomach and intestine.

The observations recorded below were undertaken in an attempt to find some practical means of overcoming the slow gastric emptying time in patients receiving high-fat diets. Our results were so much at variance with many earlier studies, that the major effort soon became one of clarifying, in our own minds, some aspects of the effect of fats upon the stomach and intestine. Because few studies have been made upon human subjects, the experiments are reported in some detail.

Material and Methods

Observations were begun upon three patients in whom gastrostomies had been performed for obstructing inoperable malignant lesions of the larynx, esophagus, and thyroid. These subjects were ideal for observing the gastric evacuation of liquid by catheterizing the artificial stomas. In attempting to extend initial observations made on these three patients by nasal intubation of normal adults, it became quite obvious that any subject so dealt with was no longer entirely normal. In several instances, the trauma of intubation and psychic stimulation affected the results in a gross manner. Although not ideal, roentgenography proved preferable to intubation as a method of conducting such observations.

The avoidance of discomfort on the part of the subject appears to outweigh the aversion to the taste and smell of the barium–fat mixture administered. To minimize objectionable qualities, a 40 per cent emulsion of peanut oil* was utilized. This preparation tastes more like chalk than oil, appears milky, and is of the approximate consistency of the barium suspension with which it was mixed.† It has been shown that such emulsions are not stable within the stomach or intestine[17] and the effect is that of the ingestion of an equivalent amount of pure oil.

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* Lipomul generously supplied by Upjohn Company, Kalamazoo, Michigan.

Six groups of patients were studied: (1) five normals who received 80 grams of emulsified fat; (2) five normals who received 40 grams of emulsified fat; (3) five patients with partial gastrectomy and gastrojejunostomy who received 80 grams of emulsified fat; (4) five patients with partial gastrectomy and gastrojejunostomy who received 80 grams of pure peanut oil; (5) five patients with partial gastrectomy and gastroduodenostomy who received 80 grams of emulsified fat; and (6) two patients with gastrojejunostomies without gastric resection, who received 80 grams of fat. In the latter group, one patient had a healed duodenal ulcer, and, in the second, a gastroenterostomy had been carried out three years previously for temporary pyloric obstruction following biliary-tract surgery. These two patients were without gastrointestinal complaints at the time our examinations were made, and they had normal patency of pylorus and duodenum, as well as the gastroenterostomy stomas. The patients with partial gastrectomies were asymptomatic when examined. All subjects on whom operations had been performed had at least one prior barium study of their upper gastrointestinal tract. The two normal groups were comprised of volunteer college students, and of hospitalized patients awaiting or convalescing from operations, such as herniorraphies and ligation of varicose veins. They were all familiar with the x-ray department and methods of examination.

Except for the normals receiving 40 grams of emulsified fat and the five gastrectomy patients receiving pure peanut oil, each subject received 80 grams of emulsified fat. The experimental meal was made up of an appropriate amount of fat mixed with 60 ml. of a barium sulfate suspension in water to make a total volume of 260 ml. The final dextrose concentration was seven per cent in each instance. All subjects were fasted overnight for approximately twelve hours. The observations were started at 8.30 A.M., and were carried out in the erect position. After preliminary orientation by the examiner, the subject drank one large mouthful of the meal, and its passage through the esophagus into the stomach and intestine was noted. Within two minutes, the remainder of the meal was swallowed under continuous fluoroscopic observation. The effect was observed during five additional minutes and, at eight to ten minutes from the initial swallow, an abdominal film was taken with the patient prone or recumbent. Thereafter, the patients sat in the waiting room, read, smoked, and viewed television. At intervals, additional films were obtained for observation of gastric evacuation. They were not told that the meal contained ingredients other than barium and, except in the group that received unemulsified oil, none identified fat as a constituent of the mixture they had ingested.

The amount of opaque material remaining in the stomach was estimated, and the progress of the meal down the intestine was noted from the films.

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† The emulsion had the following composition—peanut oil 40%, phosphatide 2%, triton 0.2%, dextrose 10%, and sodium benzoate 0.1%.

This method of measuring the amount of gastric residue would not be accurate enough for precise quantitative studies, but, since the differences among groups were large, the method proved admirably suited to provide an answer to the present problem.

Results

Group 1 (normal subjects who received 80 grams of emulsified fat). On ingestion, the first mouthful of the meal passed into the cardiac portion of the empty stomach, and thence down the lesser curvature. It was impossible to determine whether it was moved along by gravity or peristaltic activity. The bolus passed immediately into the duodenal cap, and stopped abruptly. The cap remained filled from that time forward. In two subjects, a trace of opaque material passed on down to the second portion of the duodenum, but, in the remaining three, no trace of the meal was detected beyond the duodenal cap during the period of fluoroscopic observation. On taking the remainder of the meal, the stomach, which had hitherto shown weak peristalsis, became quiet. Occasionally, a few weak peristaltic waves traversed the antral region for a minute or two before fading out. Thereafter there was no change. Manual palpation, deep breathing, coughing, and straining did not force stomach contents into the duodenum.

The rate of evacuation from the stomach is recorded in TABLE 1. In three of the five subjects, no portion of the meal passed the pylorus-duodenal-cap region during the first eight to ten minutes. At the end of one hour, there was either no evacuation or an insignificant amount. At the end of two hours, the stomach still contained all but a small fraction of the meal (60–95 per cent). At the end of four hours, three subjects still retained an estimated 40, 50, and 80 per cent of the original volume. In four subjects, the normal shape of the stomach was maintained, with the size accommodated to the fluid content. The films demonstrate contraction of the antrum throughout the first hour or two after ingestion of the fat.

Group 2 (normal subjects who received 40 grams of emulsified fat). The only difference between this and the preceding group was in the intensity and duration of the response to the fat meal. In four of the five subjects, a trace of the opaque material passed into the duodenum during the initial fluoroscopic period. Thereafter, evacuation of the stomach proceeded more rapidly than after the 80-gram-fat meal, this being particularly noticeable during the third and fourth hours. At the end of four hours, a negligible amount of the opaque material remained. The rate of passage of the meal through the small intestine was approximately the same in this group as in the preceding group.

Group 3 (patients with partial gastrectomy and gastrojejunostomy who received 80 grams of emulsified fat). In this group of patients, the first swallow of the meal passed immediately through the gastroenterostomy stoma, and then quickly to the lower jejunum and upper ileum. Ingestion of the remainder of the meal filled the stomach, but there was almost continuous flow into the intestine for approximately thirty seconds. Thereafter,

TABLE 1

NORMAL SUBJECTS (40 GRAMS FAT)

	8-10 min.		60 min.		120 min.		180 min.		240 min.	
Patient	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal
1	99	Trace Duodenal Loop	99	Trace Ligament Treitz	90	Term. Ileum	70	Ascend. Colon	10	Ascend. Colon
2	99	Trace	85	Term. Ileum	70	Term. Ileum	30	Ascend. Colon	Trace	Ascend. Colon
3	99	Trace Jejunum	90	Term. Ileum	80	Term. Ileum	50	Ascend. Colon	Trace	Ascend. Colon
4	99	Trace Duodenal Loop	85	Term. Ileum	85	Term. Ileum	50	Term. Ileum	Trace	Term. Ileum
5	100	Stomach	—	—	80	Term. Ileum	—	—	10	Term. Ileum
NORMAL SUBJECTS (80 GRAMS FAT)										
1	95	Trace Jejunum	—	—	60	Term. Ileum	—	—	10	Cecum
2	100	Stomach	95	Trace Ileum	—	—	90	Ascend. Colon	50	Trans. Colon
3	100	Stomach	95	Trace Ileum	80	Ileum	—	—	80	Term. Ileum
4	100	Stomach	100	Stomach	95	Trace Term. Ileum	—	—	—	—
5	99	Trace Ligament Treitz	95	Term. Ileum	90	Term. Ileum	80	Term. Ileum	40	Ascend. Colon

the discharge from the stomach slowed and, at this phase, it was possible to observe better the mechanism by which the fluid passed through the artificial stoma. The stomach was completely quiet and, in no instance, was persistalsis observed passing across it (a similar result consistently observed with barium alone). A small amount of the meal entered the afferent loop of the jejunum, but this was swept out by the next peristaltic wave. Jejunal peristaltic waves were observed at the rate of eight to ten per minute. After the initial filling of the jejunal loops adjacent to the anastomosis, the discharge from the stomach became intermittent. The material ran into the jejunum during relaxation, was then swept along by a wave of peristalsis, after which the process was repeated. In three of the subjects, after a deep inspiration, expiration caused additional emptying. Coughing caused some evacuation in one patient.

TABLE 2 records the estimated gastric residue in the five patients of this group. The emptying time of the stomach, and the rate of progress through the small bowel were exceedingly rapid. It is of interest that the two patients who had gone the greatest length of time after operation, four and eleven years respectively, had some tendency to retain material within the gastric remnant, but even they evacuated their stomachs at a rate much faster than normal.

Group 4 (patients with partial gastrectomy and gastrojejunostomy who received 80 grams of peanut oil). These observations were made on different patients from those making up Group 3. Neglecting individual variation, there was no difference in the mechanism or rate of gastric emptying between this group that received the pure peanut oil and the group that received the same quantity of oil in an emulsified form. The rate of passage of the barium–fat meal through the small bowel appeared similar to that of the emulsion.

Group 5 (patients with partial gastrectomy and gastroduodenostomy who received 80 grams of emulsified fat). In these patients, the first portion of the duodenum had been anastomosed to the gastric remnant (Billroth I). The pylorus and duodenal cap had been excised along with the distal two-thirds of the stomach. On ingestion of the fatty meal, the stomach was quiet, as observed in the patients with gastrojejunostomies. The first swallow went immediately into the duodenum, and then quickly into the jejunum and ileum. The full stomach continued to empty rapidly, and the mechanism of emptying was even more readily observed than in the preceding group. The first sudden egress continued for approximately thirty seconds. Subsequently, material left the stomach only when the duodenum relaxed. A small portion entered the duodenal loop during each relaxation, and was then swept along by a wave of peristalsis. The duodenal peristalsis was usually of the "pendulum" type, a wave passing down every six or seven seconds. The lower small bowel was observed to be well outlined in each subject during the period of fluoroscopic observation.

The estimated gastric residues are listed in TABLE 2. The rate of emptying is even more rapid than in Groups 3 and 4. Excluding patient number three, PARTIAL GASTRECTOMY—GASTROJEJUNOSTOMY (80 GRAMS EMULSIFIED FAT)

Fluoroscopy	Patient	8-10 min.		30 min.		60 min.		120 min.		180 min.	
		Gastric residue, %	Head of meal	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal	Gastric residue, %	Head of meal
Free passage through anastomosis	1	<5	Ileum	—	—	0	Term. Ileum	0	Term. Ileum	0	Term. Ileum
	2	60	Ileum	—	—	10	Cecum	—	—	—	—
	3	10	Ileum	5	Term. Ileum	<5	Term. Ileum	0	Term. Ileum	—	—
	4	50	Cecum	—	—	20	Trans. Colon	0	Descend. Colon	—	—
	5	40	Ileum	20	Term. Ileum	15	Term. Ileum	15	Term. Ileum	—	—
PARTIAL GASTRECTOMY—GASTROJEJUNOSTOMY (80 GRAMS UNEMULSIFIED FAT)											
Delay at anastomosis for 1 minute	1	30	Term. Ileum	10	Ascend. Colon	Trace	Descend. Colon	—	—	—	—
Free passage through anastomosis	2	5	Term. Ileum	Trace	Cecum	0	Cecum	—	—	—	—
	3	10	Term. Ileum	Trace	Ascend. Colon	0	Ascend. Colon	—	—	—	—
	4	50	Ileum	40	Term. Ileum	10	Term. Ileum	—	—	—	—
	5	40	Ileum	10	Term. Ileum	Trace	Term. Ileum	—	—	—	—
PARTIAL GASTRECTOMY—GASTRODUODENOSTOMY (80 GRAMS EMULSIFIED FAT)											
Free passage through anastomosis	1	20	Term. Ileum	0	Trans. Colon	0	Rectum	—	—	—	—
	2	<5	Term. Ileum	0	Cecum	0	Trans. Colon	—	—	—	—
	3	40	Jejunum	40	Ileum	40	Term. Ileum	—	—	—	—
	4	20	Term. Ileum	<5	Descend. Colon	0	Rectum	—	—	—	—
	5	<5	Cecum	0	Descend. Colon	—	—	—	—	—	—
GASTROJEJUNOSTOMY (80 GRAMS EMULSIFIED FAT)											
Slow passage through anastomosis	1	95	Jejunum	90	Term. Ileum	90	Term. Ileum	80	Term. Ileum	10	Term. Ileum
	2	90	Jejunum	90	Ileum	70	Term. Ileum	50	Term. Ileum	—	—

who was only nine days postoperative, in each instance, the gastric remnant was empty at the end of thirty minutes. The passage of the meal through the bowel was likewise more rapid than in either the normal groups, or than in Groups 3 and 4 with gastrojejunostomies.

Group 6 (patients with gastrojejunostomies without gastric resection who received 80 grams of emulsified fat). It was possible to locate only two examples for study. Prior to our study, one patient had a barium examination which showed a normally patent pylorus and duodenum, as well as a functioning gastrojejunostomy. The extraluminal inflammation following cholecystectomy, which had caused duodenal obstruction three years earlier, had completely subsided, and the patient was asymptomatic. An unusual opportunity was afforded to examine a normal duodenum and stomach with a coexisting gastrojejunostomy. The gastrojejunostomy in the second patient had been performed six months previously for a partially obstructing duodenal ulcer, which was quiescent at the time of this examination.

In these two patients, the gastric emptying was more rapid than normal, but still greatly delayed in comparison with patients with gastrojejunostomies combined with resection. At the end of two hours, 80 and 50 per cent of the meal, respectively, remained within the stomach. No portion of the barium–fat mixture was seen to leave the stomach via the pylorus and duodenum, until the second hour in one case, and the third hour in the other. The passage of the meal through the small intestine was normal.

Discussion

It is obvious from the results recorded in TABLES 1 and 2 that, after partial gastrectomy, there is a striking difference in the gastric emptying of high-fat meals, as compared with the normal stomach. Roentgenologists have long been familiar with the rapid emptying time of the stomach remnant after partial gastrectomy and gastroenterostomy with the barium sulfate suspension in common usage.[19] The effect of fat upon the emptying time appears to have been completely lost after partial gastrectomy as a result of the elimination of the distal two-thirds to three-quarters of the stomach, the pylorus and proximal centimeter or two of duodenum in most patients. After such operations, the evacuation of high-fat meals proceeds at approximately the same rate as with the inert barium sulfate suspension.

Several possibilities are immediately apparent as explanations of this phenomenon. The exclusion of the pyloric sphincter, or perhaps the antrum-pylorus-cap functional unit,[18] is the most obvious. While other investigators have not agreed that the sphincter plays any part in the retention of high-fat meals, one cannot escape the consistent roentgenographic appearance of antral contraction that appears within a second or two after the ingestion of fat. If this suggested possibility is correct, then, in effect, partial gastrectomy removes the end organ in a reflex mediated by hormonal and/or nervous mechanisms. The evidence that the reflex can be initiated by contact of fat with intestinal mucosa seems conclusive. In the partial gastrectomy patients, however, the presence of a large portion of the fat meal in the duodenum or jejunum showed no retarding influence on the gastric evacuation of the remaining portion.

The other possibility to be considered is that the distal portion of the stomach is concerned in some manner with the initiation of response to fat, whether the fat contacts gastric mucosa or not. Evidence that such a mechanism may play a part has come from observations on three patients with postoperative nonobstructive jejunal ulceration after partial gastrectomy, in whom one can reasonably presume some antral or antral-type tissue remained (two had free acid, and one had no free acid). They responded to high-fat meals by a delay in the evacuation of the gastric remnant, and this response was completely abolished by vagotomy. The possibility of using this type of observation to determine the adequacy of partial gastrectomy, *i.e.*, antral excision, is being explored at present. There is further indication of this in Singleton's observations after pylorectomy, and in our two observations after gastroenterostomy without antral resection. In view of the known rapid evacuation of barium sulfate meals through gastroenterostomies,[19] it seems significant that our patients with such anatomical arrangements were able to retain fat meals for extended periods. Sphincteric action at the artificial stomas would seem a nebulous explanation, since both stomas were placed well up on the body of the stomach and neither roentgenographic study nor pressure measurements[10] indicate strong contracture of this portion of the stomach in response to fat.

These observations add to, and confirm those of Shay and Gershon-Cohen,[20] McCann,[21] and Thompson,[22] showing that the absence of the normal sphincteric mechanism impairs the retentive capacity of the stomach, though it does not prevent a near-maximal response in the proper situation.

Practical Aspects. In almost all patients who have had a partial gastrectomy sufficiently radical to abolish the response to fat, the use of high-fat diets should be entirely feasible and of benefit. The limitations imposed by delayed emptying in normal subjects do not exist in these patients. Patients have consistently shown an aversion to the taste and smell of undisguised fats, but their behavior within the stomach and intestine is no different from that of emulsified fats. When tolerated, butter, cream, mayonnaise, bacon, and similar foods should suffice equally as well as emulsions of fat. In choosing diets for patients after gastrectomy it should be remembered, however, that one is in effect selecting a diet for jejunostomy feeding because the remaining stomach functions more as a conduit than an organ for storage.

The passage of the barium-fat meal down the intestine has been recorded in TABLES 1 and 2. Normally, transit into the lower ileum is rapid, but thereafter, in most instances, the meal remains for an hour or two. The position of the meal, as recorded in the tables under "Head of meal," is somewhat misleading, since that refers to the most distal advancement of the opaque material, whereas usually the principal part of the meal remained in the ileum. With the exception of the patients with gastroduodenostomies, the rate of passage of the meal through the small intestine seemed about the same in each group. The normal stomach empties itself rather rapidly once the delaying effect of the fat has lessened. However, it would appear from the animal experiments of Emery that the sudden entrance of a large fatty meal into the jejunum or duodenum after gastrectomy is undesirable and leads to moderate impairment of fat absorption.[23] We have no explanation for the excessively rapid emptying and transit through the intestine after the Billroth I operation.

The Effect of Dosage. It is apparent from the results recorded in TABLE 1 that the amount of fat ingested bears a direct relationship to the emptying time of the normal stomach. Only two different doses were used, but the results are sufficient to confirm McSwiney's and Spurrell's animal observations. While large, the 40-gram meals appear to be within a range that can normally be evacuated within a four-hour period, and it is quite obvious that twice that amount delays gastric emptying to an extent that prohibits its use clinically.

Summary

The introduction of a high-fat meal into the normal stomach results in delay in gastric emptying. This effect is abolished by partial gastrectomy, if sufficiently radical to remove all antral tissue. Under these circumstances, the gastric remnant functions more as a conducting tube than as an organ of storage. While not exclusively so, the antrum-pylorus-cap sphincteric mechanism is important in producing the normally great delay in gastric emptying after a high-fat meal.

The above studies indicate the feasibility of using high-fat diets for caloric supplementation in partially or completely gastrectomized patients.

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ABSORPTION OF ORALLY ADMINISTERED EMULSIFIED LIPID IN PANCREATIC INSUFFICIENCY IN INFANTS AND CHILDREN

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The particulate theory of lipid absorption, while denying that complete lipolysis is a necessary prerequisite for fat absorption, nevertheless demands the presence of an active lipase in the intestine for the production of mono- and diglycerides. These are necessary for emulsification.[1–3] In patients with fibrosis of the pancreas, in whom all pancreatic ferments including lipase are absent,[4] the absorption or orally ingested fat[5, 6] and vitamin A is deficient.[7] Furthermore, emulsification within the intestinal lumen is defective.[8] When vitamin A is emulsified prior to administration to such patients, its absorption becomes normal.[7, 9–11] Although commercially available pancreatin contains but modest amounts of lipase when it is fed with vitamin A to patients with fibrosis of the pancreas, there result normal absorption curves.[7] This same material also improves fat absorption in patients with achylia pancreatica.[12–14]

On the basis of these observations, it seemed reasonable to investigate whether the administration of dietary lipids already emulsified would improve intestinal absorption by patients with achylia pancreatica. Since pancreatin[13, 14] may decrease appetite,[15] it seemed desirable to compare fat absorption with and without pancreatin, not only on a percentage basis, but also the grams of fat absorbed on an *ad-libitum* intake.

Plan of Experiments. Four patients with fibrosis of the pancreas were studied for 16 balance periods. Cows' milk was used as the menstruum for fat administered in each instance. During control periods, ordinary whole cows' milk with 3.5 per cent butter fat was fed. After four periods of 10–14 days, quantitative stool collections were obtained. In each subject, subsequent balance studies were performed either with homogenized milk and/or two different fat emulsions. Three patients were also studied while receiving pancreatin. In each instance, stool fat was determined. During nine periods, stool nitrogen was measured and, in four of these, the urinary nitrogen was also determined. An attempt was made to keep the fat intake constant from period to period in a given subject, except between periods 9 and 10 and periods 15 and 16. During these periods, the subjects were fed *ad libitum*, with the intent of observing whether improvement in absorption obtained with pancreatin was counterbalanced by decreased intake.

The details of these balance periods, including composition of the emulsions can be obtained by inspection of TABLE 1. The particle size of the artificial emulsions used was measured microscopically and was found to be generally below 0.5 μ.

Methods. The procedures with regard to performance of balance studies as well as laboratory determinations were identical with those previously reported.[16, 17]

TABLE 1

BASIC DATA (VALUES PER 24 HOURS)

Period no.	Patient	Age, mos.	Wt., kg.	Diet	Days balance period	Intake					Output			Fat absorbed, %	Balance	
						Cal./kg.	Fat, g.	Fat, g./kg.	N, g.	N, g./kg.	Fat, g.	Nitrogen, g. Stool	Nitrogen, g. Urine		N, g.	N, g./kg.
1	VP	8	5.3	*a*	3	155	35	6.6	5.6	1.06	14.8	2.18	—	61	—	—
2	VP	8	5.5	*b*	3	146	35	6.4	5.6	1.02	12.9	1.90	—	63	—	—
3	VP	8	5.6	*b, c*	3	149	35	6.3	5.6	1.00	9.8	1.37	—	72	—	—
4	VP	8	5.9	*d*	3	105	35	5.9	5.6	0.95	12.0	—	—	66	—	—
5	VP	24	8.1	*b*	4	122	33.9	3.5	6.4	0.79	19.4	—	—	43	—	—
6	VP	24	7.8	*e*	4	132	36	4.6	6.0	0.77	24.7	—	—	31	—	—
7	JM	3	3.6	*b*	3	192	34.7	9.6	5.6	1.56	13.0	1.50	—	63	—	—
8	JM	3	3.7	*d*	3	180	38.3	10.4	7.7	2.08	17.6	3.93	—	54	—	—
9	JM	3	3.7	*b, f*	3	210	28.4	7.7	4.6	1.22	16.0	0.48	2.24	44	1.83	0.49
10	JM	3	4.2	*a*	3	270	48	11.4	7.7	1.83	23.3	2.19	1.97	52	3.50	0.83
11	NA	12	7.2	*e*	4	144	36	5.3	6.4	0.89	14.1	—	—	61	—	—
12	NA	12	6.9	*b*	4	124	25.8	3.8	5.6	0.80	16.1	—	—	38	—	—
13	WH	18	7.6	*b*	4	147	34.4	4.5	8.2	1.08	20.3	—	—	41	—	—
14	WH	18	7.9	*e*	4	161	38.6	5.0	9.1	1.15	22.0	—	—	43	—	—
15	WH	18	8.6	*b*	4	198	60.5	7.1	12.5	1.45	36.1	5.73	3.85	40	2.92	0.34
16	WH	18	10.3	*b, g*	4	137	51	4.9	11.7	1.13	14.0	1.45	7.13	73	3.12	0.30

[a] Homogenized milk, 3.5% butter fat.

[b] Whole cow's milk, 3.5% butter fat.

[c] Pancreatin, 4 g./24 hr.

[d] Special emulsion no. 1. 10% olive oil and 5% purified egg lecithin. This was mixed with skimmed milk to yield a solution containing 3.5% fat. Supplied through the courtesy of Dr. Warren M. Cox of the Mead-Johnson Company.

[e] Special emulsion no. 2. 40% vegetable oil, 10% dextrose, and 2% soybean phosphatid. This was mixed with skimmed milk to yield a solution containing 3.5% fat. Supplied through the courtesy of Dr. E. L. Burbidge of the Upjohn Company.

[f] Pancreatin, 2.6 g./ 24 hr.

[g] Pancreatin, 10 g./ 24 hr.

Results. Artificial emulsions were well taken and well tolerated by the patients. The emulsion used in periods 4 and 8 seemed to cause an increase in the number of stools passed, but this never approached frank diarrhea.

The following observations may be made from inspection of the data contained in TABLE 1 and FIGURES 1 and 2. Each patient had substantial steatorrhea. At best, the administration of pre-emulsified lipids resulted in an irregular and perhaps insignificant increase in fat absorption over that observed following ingestion of nonemulsified lipid. Except when pancreatin was administered, stool nitrogen was greater than 1.5 grams per day in those patients in whom it was measured.

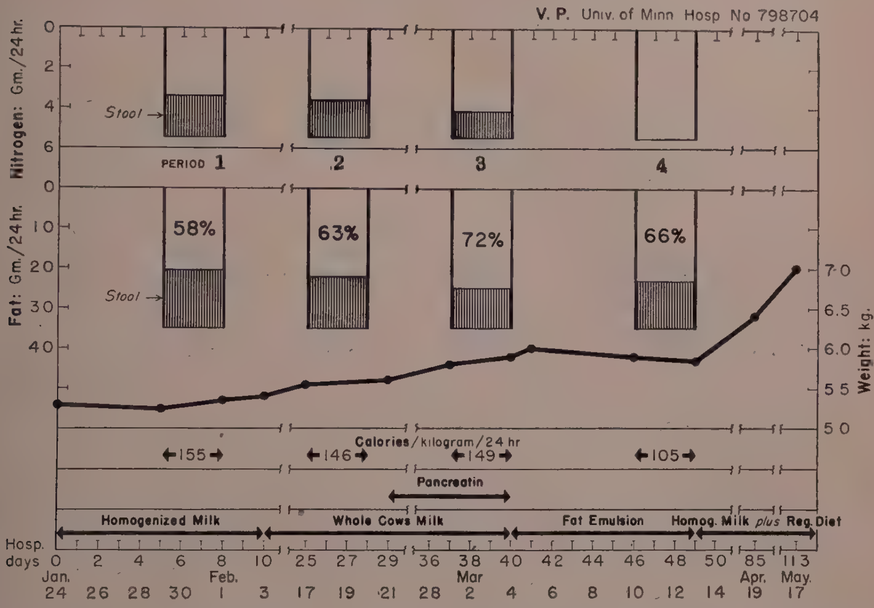

FIGURE 1. Fibrosis of the pancreas—effect of pancreatin, homogenized milk, and a fat emulsion on nitrogen and fat absorption. Patient V.P., 8.5 months (Periods 1–4). Period 1, homogenized milk. Period 2, whole cow's milk. Period 3, whole cow's milk plus pancreatin, 4 grams per 24 hours. Period 4, special emulsion, composed of five per cent olive oil and five per cent gelatin, added to skimmed milk and made isocaloric with the diet given during the previous periods by the addition of glucose.

Note. (1) Azorrhea. (2) Steatorrhea. (3) Failure to demonstrate any conspicuous improvement in fat absorption during two periods when homogenized lipids were given, Periods 1 and 4. (4) Improvement in fat and nitrogen absorption while receiving pancreatin. (5) High-caloric intake offered. (6) High-fat intake given throughout period of study. (7) Gain of 1.3 kilograms in 65 days while receiving regular diet *ad libitum.*

Conclusion. No improvement in fat absorption was demonstrated with the use of homogenized lipid. Although pancreatin resulted in an improvement in fat absorption and nitrogen absorption, it did not cause any notable change in the rate of weight gain.

Pancreatin administration resulted in an irregular improvement in per cent fat absorption. When the fat intake was kept constant between the control and pancreatin periods, this was significant (see period 2 *vs.* period 3). When there was no restriction on food intake, the improvement in fat absorption varied. Between periods 15 and 16 it rose from 40 to 73 per cent and the grams of fat absorbed rose from 24.5 to 37. This occurred in spite of a substantially greater caloric and fat intake during the period without pancreatin. With considerably lower levels of pancreatin administration, the improvement in fat absorption, both on a percentage and absolute basis, was not in evidence. Between periods 9 and 10 the fat absorption actually fell. However, the adverse effect of pancreatin on appetite was still demonstrated.

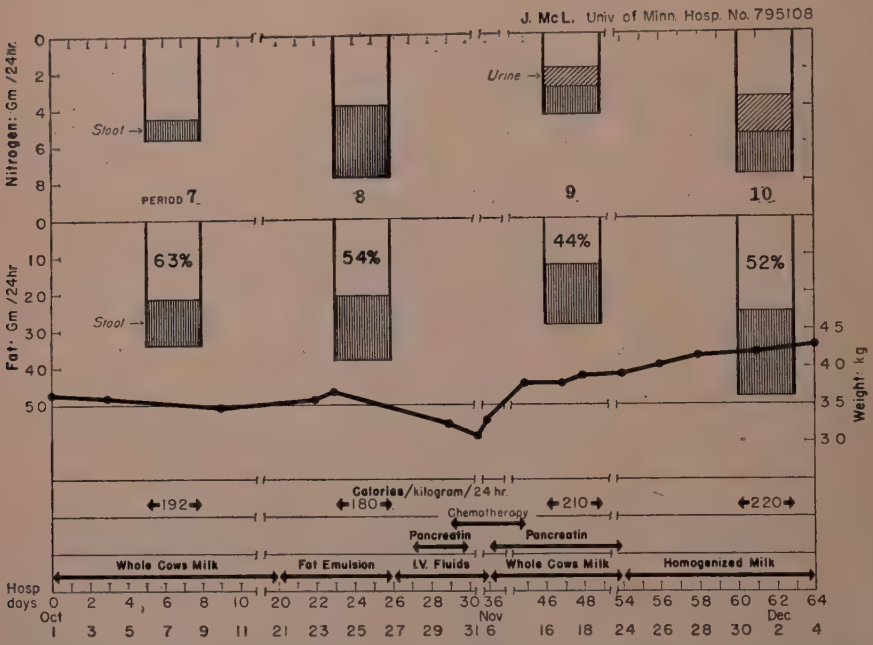

FIGURE 2. Fibrosis of the pancreas—effect of pancreatin, homogenized milk, and a fat emulsion on nitrogen and fat balance. Patient J.McL., 3 months (Periods 7–10). Period 7, whole cow's milk. Period 8, a special emulsion composed of five per cent olive oil and five per cent gelatin, added to fat-free milk and made isocaloric with the formula used during other periods by the addition of glucose. Period 9, whole cow's milk plus pancreatin, 2.6 grams per day. Period 10, homogenized milk.

Note. (1) Conspicuous azorrhea. (2) Steatorrhea. (3) Failure to demonstrate improved fat absorption with the special emulsion, due particularly to the development of diarrhea. (4) The improvement of fat absorption while receiving homogenized milk (Period 10), when compared to absorption while receiving pancreatin (Period 9). (6) The occurrence of respiratory infection during this period of the study caused frank diarrhea and weight loss. This responded to chemotherapy. (7) Pancreatin caused decrease in stool nitrogen. (8) Nitrogen balance was less during Period 9 than it was during Period 10. (9) Weight gain was poor on whole cow's milk and on the special emulsion, but improved on pancreatin, and this improvement continued without pancreatin, while receiving adequate calories and homogenized milk.

Conclusion. It was impossible to demonstrate improved fat absorption with the use of emulsified lipids. Although pancreatin caused improved nitrogen absorption from the gut, it did not cause an improved fat absorption or higher nitrogen balance. Since the patient was fed *ad libitum* in both Periods 9 and 10, pancreatin seemed to cause a decrease in appetite.

One further observation, not entirely unexpected, was made when comparing the nitrogen balance with and without pancreatin. Although the nitrogen absorption was higher when pancreatin was administered, the nitrogen balance was not substantially improved. Apparently the increased amount of nitrogen absorbed was largely re-excreted in the urine.

Discussion

Improvement in fat absorption due to any experimental regimen can only be measured in subjects with steatorrhea. The rationale for administration of emulsified lipid to any patient must lie in the observation that emulsification within the intestine is deficient. Only in patients with these two abnormalities, might one expect enhanced absorption by use of fat emulsions. Individuals having absent pancreatic lipase should offer ideal subjects for observations on this problem, having as they do steatorrhea[5, 6] and deficient emulsification.[8] The fact that, in the experiments presented, emulsification was without obvious benefit, might be related less to the unsuitability of the subjects or a defect in the particulate theory of fat absorption than to the possible instability within the stomach of the emulsions tested. This factor was not assayed in the present experiments.

Pancreatin has been demonstrated by others[12, 13, 14] to improve fat absorption in achylia pancreatica. The means by which it affects this improvement is not entirely explained since its lipase potency is low and irregular.[7] It seems possible that it may act as an emulsifying agent within the bowel and by this mechanism improve fat absorption. Failure to demonstrate an improvement in fat absorption in period 9, when pancreatin was administered, most probably was due to an inadequate dose level. Wollaeger and his coworkers[13] indicated that a generous intake of pancreatic substance was necessary for substantial benefit to be achieved. The effect on appetite, however, was not lacking at this dose level.

On the basis of the results presented above, it might seem logical to continue a search for a better emulsion for use in patients with achylia pancreatica. When this is prepared, one might anticipate that improved absorption will be demonstrated. For the present, homogenized milk, fed *ad libitum*, might be the cheapest source of an emulsion. Although high dosage levels of pancreatin might significantly improve fat absorption, the effect on appetite may vitiate this improvement. Low levels of administration certainly will do that.

Conclusions

In four children with fibrosis of the pancreas, the administration of preemulsified lipid did not result in a clearly significant improvement in intestinal absorption over that observed with a similar amount of unemulsified lipid. Three different types of emulsions were used and none was more successful than the other. Pancreatin increases percent fat absorption but, on an *ad libitum* intake, the actual grams of fat absorbed may not substantially increase. Furthermore, although nitrogen absorption improves with pancreatin, the actual amount retained apparently does not.

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ORAL FAT EMULSIONS COMBINED WITH PROTEIN SUPPLEMENTS IN THE MANAGEMENT OF ACUTE POLIOMYELITIS*

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Recent developments in food supplements are contributing to improved clinical results in the treatment of poliomyelitis, which, by our concept, is a systemic disease of virus etiology. The various poliomyelitis or poliomyelitis-like viruses thus far identified have a special predilection for the central nervous system and for the voluntary muscles.

Clinically, poliomyelitis is classified as either abortive, nonparalytic, or paralytic. The paralytic types may be spinal, bulbar, or encephalitic, in the order of their greatest frequency. Only in the abortive types is recovery spontaneous and apparently complete.

The older therapeutic approach emphasizes immobilization and prolonged bed rest with no special nutritional care. Characteristic of the results are a high incidence of ankylosis, marked permanent muscle atrophy, prolonged malnutrition and a high incidence of orthopedic operations. The approach we use[1] combines (1) early ambulation; (2) muscle relaxation by curarization[2] and active exercise program,[3] (3) extended medical supervision; and (4) special nutrition.[4] In our opinion, this has given us superior clinical results, such as reduced severity of the acute phase, minimal weight loss, minimal disabling atrophy and ankylosis, accelerated convalescence, shorter hospitalization, reduced incidence of corrective surgery,[5] and favorable results in functional restoration.

In this presentation, I shall attempt to outline the special nutrition—one of the four important measures upon which our treatment of polio is based.

During the past three years, we have used hyperproteinization[6] with a high caloric intake to enhance utilization and to spare the body protein. At first, this high caloric intake was supplied by carbohydrates, but, during the last year, the extra calories have been supplied by oral fat emulsions[7] which have the additional advantages of rapid assimilation and weight gain.

Each patient's physical status was evaluated, and a diet was ordered consisting of easily assimilated protein preparations, protected by adequate caloric coverage, in quantities to attain a level of at least four grams of protein per kilo body weight, fortified with fat emulsion. In this way, from 100 grams or more of protein, and 500 or more calories in fat were added to the diet. To do this effectively, it was necessary to give between-meal feedings. Vitamins and minerals were ordered as needed. High-caloric protein drinks were also utilized for supplementation, since the optimum

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* The Upjohn Company very kindly supplied all of the fat emulsions, Lipomul, used in this study. The author is indebted to the Upjohn Company for supplies of Somagen Solubilized, and to Humanic Brands, Inc. for supplies of Provimalt.

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high intake of protein advisable cannot always be attained on the usual diet. The limiting factors are the bulk required, and the lack of stomach capacity for the extra-large amount of food. Other limiting factors may be anorexia, and the lack of sufficient strength to chew the food, under which circumstances the patient's only desire may be for liquid foods and beverages.

The oral fat was added to the milk together with the protein supplement, and, to make the preparation more palatable, sugar and vanilla or chocolate syrup (depending on the patient's preference) were added. There were some complaints of fullness of the stomach, but this was not a serious problem. The majority of patients preferred the drink after a meal or at bedtime. The cooperation of the nursing staff[8] and dietetic department is essential, as every tray is checked after it leaves the patient, any food not eaten being made up in an extra meal at night.

In most other regimens, during the acute fever stage, the patients are placed on a liquid diet or on parenteral fluids, both of which are always inadequate nutritionally. With our program, we supply all the necessary nutrients parenterally by giving glucose, protein, blood, and sometimes plasma, and orally by giving protein and fat emulsions.

After the acute phase, the patients are fed the general hospital diets, which are calorically adequate, but which, according to "Therapeutic Nutrition",[9] are inadequate in proteins. In checking the food trays after the patients had eaten, it was noted that at no time was all the food eaten, especially in the children's wards.[10] Meat, chicken, vegetables, broths and soups, cottage cheese, and salads were seldom touched. Scrambled eggs were usually scrambled a little more extensively, and left on the plate, while mashed potatoes were eaten partly. Jelly sandwiches were preferred. As a rule, cereals, desserts, bread and butter, and milk were consumed first. Fruit juices were usually taken well, but soft drinks, when available, had a high priority in upsetting the stomachs of the patients.

One of the main problems in poliomyelitis is wasting of muscle tissue. This wasting may arise from several factors: (1) dietary inadequacy; (2) fever, anorexia, nausea, and vomiting in the course of the acute phase; (3) the catabolic period attributable to the oversecretion of catabolic hormones by the adrenals as part of the stress reaction; (4) immobilization of the patient; and (5) the destruction of tissue cells by the infecting virus. The first three have been shown to be reversible through raising the level of feeding. Whether (4) and (5) are reversible has yet to be determined.

In the past, it was generally accepted that loss of weight was inevitable, the disease destroying the anterior horn cells, and thus producing muscle atrophy by denervation. In following the patients from the onset to complete functional restoration in our clinic, we have noted that they lost a great deal of weight, those with the most extensive paralysis suffering the greatest loss (averaging 10 to 40 pounds during the first three to six weeks). Because of this rapid early loss of weight, it is imperative to start the feeding as soon as the patient is admitted to the hospital. As a result of our nutritional program, we have succeeded in having a large number of our patients maintain or gain weight during their hospitalization. This program is continued on ambulatory patients until maximum muscle strength and function have been attained. It must be emphasized here, that our object is not to have the patient gain weight *per se*, but rather to maintain his muscle bulk and muscle strength without the deposit of excess flabby fat. Excess fat in the presence of weak or paralyzed muscles is a liability which we always try to avoid by diet and exercise.

Total urinary nitrogen, urinary creatine excretions,[11] and blood chemistry were done on a number of patients during this study. Daily weights were taken at the same time each day.

Too often one does not realize that increased nutritional intake is very essential for the acute and convalescent poliomyelitis patient. In addition to the factors already mentioned, we should not forget that the muscle metabolism is seriously disturbed. There is the possibility that the muscle tissue may be directly attacked by the virus.[12] The extensive muscle spasm,[13, 14] which is always present, interferes with the circulation, and thus nutrition of the muscles. The energy-producing or controlling factors, such as adenosinetriphosphate, phosphocreatine, acetylcholine, and hemoglobin are probably interfered with. Blood sludging[15, 16] and increased capillary permeability further disturb the muscle nutrition. CoTui and others have emphasized the value of hyperproteinization in maintaining positive nitrogen equilibrium in muscle-depleting diseases. Cannon,[17, 18, 19] demonstrated the relationship of kind and amount of protein diet to antibody synthesis and to resistance to infection. Mills and Cottingham[20] (1943) reported that, for rats, the optimal phagocytic activity is definitely influenced by the temperature and by the amount of protein consumed. Kornberg[21] (1946) found that rats fed upon a protein deficient diet develop granulocytopenia, while Guggenheim and Buechler[22] (1946–1948) concluded from their studies that:

(a) The humoral defense mechanism appears to be more sensitive to protein deficiency than the cellular defense mechanism.

(b) Different food proteins elicit different bactericidal and phagocytic powers. This quality of promoting the antibacterial defense corresponds roughly to the growth promoting quality of the respective proteins.

Sherwood[23] emphasizes the importance of protein nutrition in improving one's resistance to infection by pointing out that:

(a) Antibodies are protein in nature.

(b) It takes 4 to 8 weeks to deplete the protein reserves of the rat.

(c) Immune globulin is dependent upon the protein reserves and protein intake for its formation.

Rodriquez, *et al*[24]state that, in a case of avulsion of the brachial plexus, recovery of the muscles of the arm should be expected in approximately 24 months. If this does not occur, the assumption would be justified that, regardless of the physical therapy program (three times a week), the morphologic, histologic, chemical, and other necessary properties of the muscle were not maintained in a sufficiently optimal state long enough for function to return, even though regeneration of the nerve might very likely have taken place. These authors very properly bring out a point we have been trying to emphasize,[25] namely, the tremendous importance we must place in the maintenance of optimal muscle physiology by correcting the underlying biochemical and physiologic disturbances. This we have been attempting to do[26] by directing our attention to early ambulation, muscle relaxation by curarization and an active exercise program, extended medical supervision, and special nutrition, the latter being fortified by oral fat emulsions[27] combined with protein supplements.

Summary

With our nutritional regimen, we supply the protein depleted poliomyelitis patients[28, 29] all of the needed protein and caloric requirements in easily assimilated food of high nutritional value. This is started immediately upon admission to the hospital.

It is generally accepted that hypoproteinemia in humans and animals reduces their ability to produce antibodies.[30, 31] The proteins fed replenish the body with its nitrogenous-tissue-building metabolites, which are so rapidly lost by the patients. Another important consideration is that the proteins themselves are a rich source of globulinantibody-building material, which the patient needs to overcome his virus infection.

The oral fat emulsions generate heat and energy with very little demand on the digestive system. The new chocolate flavored Lipomul is superior in tolerance and acceptability to the plain fat emulsions. This insures a palatable supplement of high caloric value, which makes possible full utilization by the body of every gram of protein given. Oral fat emulsions are proving to be very useful food supplements in high-caloric diets.

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LABORATORY AND CLINICAL STUDIES FOLLOWING THE USE OF AN ORAL FAT EMULSION

By S. D. Jacobson

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The potential advantages of fat as a caloric supplement are clear. It has been the general experience, however, that the more commonly used dietary supplements of fat have not been sufficiently palatable to permit their extensive use for this purpose. Recently, there has become available an oral fat emulsion, containing 40 per cent vegetable oil and 10 per cent dextrose, which is said to be reasonably well tolerated.* One hundred cubic centimeters of this preparation provide approximately 400 calories. We were interested in testing the suitability of this preparation as a caloric supplement for chronically ill patients. It was also considered important to see if dietary supplementation of fat would influence the standard liver-function tests commonly employed. With this purpose in mind, we administered Lipomul to thirty-five chronically ill patients.

Procedure

Each of the subjects in this study was a patient in the chronic division of the hospital for whom caloric supplementation was desirable. Four of the patients had cirrhosis of the liver, the diagnosis having been established by standard historical, physical, and laboratory criteria, as well as by liver biopsy. In the remaining thirty-one patients there was nothing to suggest impaired liver function. They had either advanced rheumatoid arthritis, or hemiplegia following cerebrovascular thrombosis. All patients were at bed rest during the entire period of observation.

The patients received a uniform diet for one week before and during the period of supplementation. This diet consisted of 300 grams carbohydrate, 100 grams fat, and 100 grams protein, providing a total of 2500 calories daily. After the patients had received this diet for one week, the oral fat emulsion was added to the daily food intake. The supplement consisted of 240 cubic centimeters of Lipomul, representing an addition of 96 grams of fat or 960 calories to the basic diet.

The following clinical laboratory tests were made before and during the period of Lipomul feeding: cephalin flocculation test; thymol turbidity test; determination of serum proteins; and bromsulphalein retention 45 minutes after the injection of five mg. per kilo of the dye. The mount of dye present in the serum was measured with a photoelectric colorimeter. In addition, the patients were weighed at weekly intervals during the period of observation.

Results

In general, Lipomul was well tolerated by most of the patients in the amounts used. This is indicated in TABLE 1.

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* Lipomul-Oral was supplied by the Upjohn Company, Kalamazoo, Michigan.

TABLE 1

No. of patients	Duration of feeding	Acceptability
5	1 day	Poor (discontinued)
7	1 week	Good
2	2 weeks	Good
11	3 weeks	Good
2	4 weeks	Good
8	6 weeks	Good

In the five patients in whom feeding was discontinued because of poor acceptability, the complaints were all either nausea or mild diarrhea which prompted them to refuse further supplementation. The remaining 30 patients tolerated the material. It was of interest that the supplementation did not reduce the appetite of the patients, so that they had no difficulty in eating the basic diet. In a few instances, the supplements of 60 cubic centimeters Lipomul were administered between rather than immediately following meals. This seemed to make no difference with respect to either acceptability or effect upon appetite.

Increase in weight was experienced during the period of Lipomul supplementation. In TABLE 2 are indicated the weight gains of the eight patients whose supplementation was six weeks in duration.

TABLE 2

Initial weight, lb.	After 6 weeks, lb.	Initial weight, lb.	After 6 weeks, lb.
167	173	129	136
128	136	103	107
136	145	98	103
106	111	112	116

Definite increase in weight was also observed in those patients whose period of fat supplementation was less than six weeks in duration, but the changes were of lesser magnitude.

In general, no significant changes were noted in the cephalin flocculation test, thymol turbidity test, and the serum protein concentration during the period of Lipomul supplementation, but in the four patients with known liver disease, and in seven patients with no known liver disease, changes in the BSP retention were noted which were in excess of technical error.

In TABLE 3 are recorded the results of the BSP tests before and during Lipomul administration in the seven patients who had no liver disease. The figures represent the percentage of dye retained in the blood 45 minutes after injection.

Although there was variation in BSP retention on subsequent weeks, there was a definite trend towards significant retention during Lipomul administration. This subsided during the latter part of the period of supplementation. Within two weeks after the fat supplementation was discontinued, no BSP retention was demonstrated in the above patients.

TABLE 3

Patient	*Before Lipomul*	*1st week*	*2nd week*	*3rd week*	*4th week*	*5th week*	*6th week*
1	0	3	8	8	17	5	7
2	3	7	14	6	6	10	5
3	0	4	0	7	3	4	5
4	0	0	0	4	5	3	5
5	0	0	0	3	5	2	1
6	0	5	2	2	5	2	4
7	0	1	8	16	—	—	—

In TABLE 4 are recorded the results of the BSP tests before and during Lipomul administration in the four patients who had cirrhosis of the liver. The figures represent the percentage of dye retained in the blood 45 minutes after injection.

TABLE 4

Patient	*Before Lipomul*	*1st week*	*2nd week*	*3rd week*	*4th week*	*5th week*	*6th week*
1	12	22	16	22	17	15	11
2	28	50	40	33	36	42	40
3	8	32	52	0	—	—	—
4	4	12	8	16	0	—	—

In this group of patients, the changes in BSP retention were more marked and appeared sooner after the beginning of Lipomul supplementation than was evident in the patients who had no known liver disease. In Patient no. 1, the degree of BSP retention tended to return to its initial value during the supplementation of the diet with Lipomul. In Patients nos. 3 and 4 BSP retention became zero during the period of observation. Despite the marked fluctuations in BSP retention noted above, there was no clinical or other laboratory evidence of deterioration of liver function in any of the above patients.

Discussion and Summary

The observations reported justify the conclusion that Lipomul, in amounts up to 240 cubic centimeters daily, is well accepted and constitutes an adequate caloric supplement in most patients requiring such supplementation. Its value seems to be enhanced by the fact that in these amounts it does not impair the appetite to any significant degree.

The data presented are inadequate to explain the fluctuations observed in BSP retention in either the cirrhotic or noncirrhotic patients. The facts that there were no clinical or other laboratory findings which paralleled the increases in BSP retention, and that, in several instances, BSP retention decreased subsequently, while fat supplementation continued, suggest that, under the circumstances of this study, the BSP test may not represent a true measure of the excretory function of the liver. Further work will have to be done to elucidate this point.

FORCED HIGH-CALORIC LOW-PROTEIN DIET IN THE TREATMENT OF UREMIA*

By W. J. Kolff

Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio

Experimental evidence in favor of a forced, high-caloric, low-protein diet in the treatment of uremia can be considered from two aspects.

(1) Deleterious effects of large amounts of protein on the normal kidney,[24] the diseased kidney,[1, 10, 27] and on the kidney reduced in size.[2] For example, Newburgh[24] fed rabbits with the whites of several hardboiled eggs per day. Albuminuria and renal injury followed a prolonged feeding with different proteins, and resulted in Bright's disease.

Smadel and Farr[10, 26] produced nephrotoxic (Masugi) nephritis in rats, which afterwards were kept on different isocaloric diets. After 8½ months, 12 of the rats on a low-protein diet were alive and well (one showed residual proteinuria). Every animal on the high-protein diet however, developed progressive nephritis, 13 of the 15 animals succumbing to renal failure within 11 months.

(2) Deleterious effects of protein on the metabolism of animals with reduced kidney substance[1, 12] or diseased kidneys,[2] and in nephrectomized animals.[3, 21, 23] For example, Addis, *et al.*,[1] resected three-fourths of the renal tissue in rats. During the first week after the operation, the death rate varied with the amount of protein consumed. There were no deaths when no protein was given, 13 per cent after 1.67 grams, and 43 per cent after 2.38 grams of protein per day. The urea content of the rats which died averaged 500 mg. per 100 grams.

Lyon, Shafton, and Ivy[21] force-fed (bilaterally) nephrectomized dogs with bread, milk, and lactose. The daily diet contained approximately 1400 calories and 30 grams of protein, and the mean survival time was 137 hours as compared to 105 hours for dogs on an *ad libitum* meat diet. Failure to maintain uniform electrolyte or caloric balance vitiated some of the earlier experiments. Thus, some animals, especially those on meat diets, died of potassium intoxication, and others simply refused to eat and metabolized their own proteins with the same result. Masson, Corcoran, and Page[23] have avoided these complications. Bilaterally nephrectomized rats were force-fed twice daily by gavage. Groups individually maintained on protein, carbohydrate, or fat, and a fasting group were compared in terms of survival time and azotemia. Survival times decreased as azotemia increased. Fasting was as deleterious as protein feeding. Survival was prolonged and azotemia lessened in carbohydrate- and fat-fed animals as compared to those fed protein or fasted. For example, in one group of 20 animals given carbohydrate, the average survival was 93 hours, while a group on protein survived only 53 hours. The beneficial effects of the nonprotein diets were abolished

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* The author is indebted to Dr. A. C. Corcoran for reviewing this manuscript.

by provoking a turpentine abscess. This experimentally supports the clinical observation[5] that infections impair the beneficial effect of diet. Apparently, the protein catabolism provoked by infection is not responsive to protein-sparing diets.

As yet, the significance of re-utilization of catabolic nonprotein nitrogen has not been assessed in man, or in its implications in experimental uremia. Ruminants have long been known to utilize nonprotein nitrogen. Laboratory rats on a nonprotein diet, deficient only in nonessential amino acids, can use the nitrogen of ammonium salts and certain other compounds in metabolism and growth.[28] Nitrogeneous metabolites thus re-used would not demand excretion and, in so far as they contribute to the uremic syndrome, acceleration of their re-utilization may turn out to be a means of therapy.

In brief, protein feeding (1) can damage residual or even normal renal

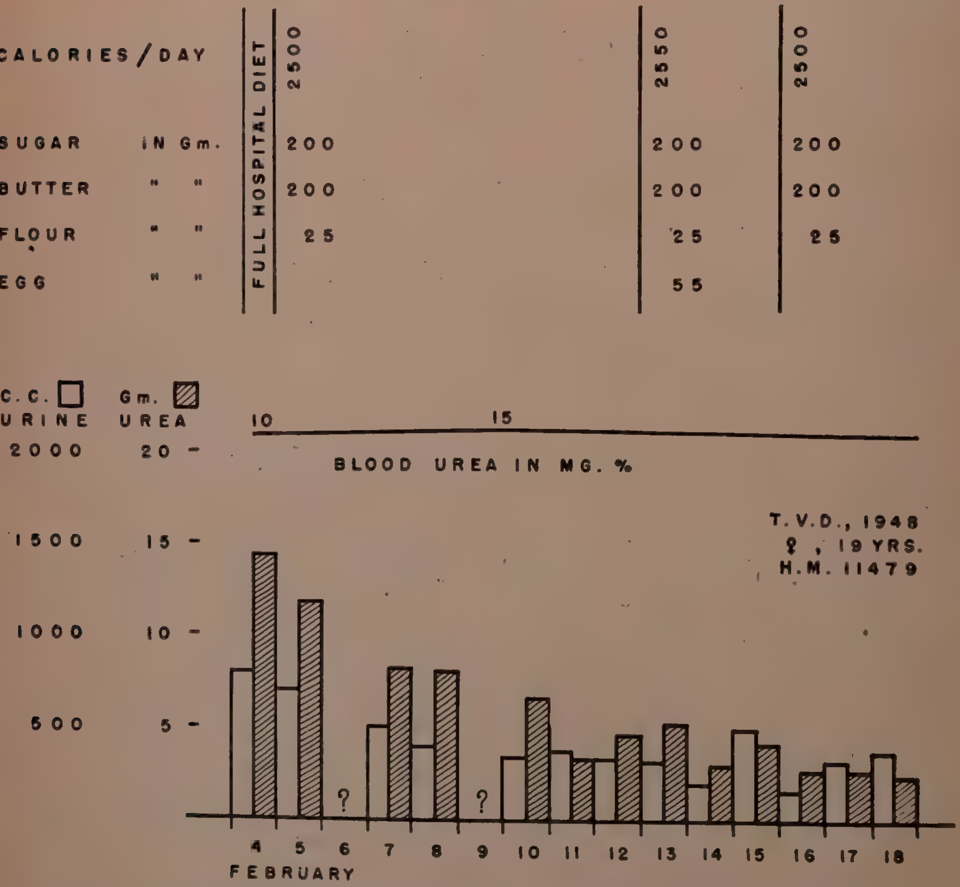

FIGURE 1. A physically healthy girl of 19 years was placed on a diet of 200 grams each of butter and sugar, made up as an emulsion, with a little flour. The ration provided 2400 calories and virtually no protein. Daily urea excretion is shown in the shaded blocks at the bottom of the graph to decrease to as little as 3 grams.

tissues, and (2) it definitely speeds death in uremia after total nephrectomy. In this respect, fasting is as deleterious as protein feeding, while the protein-sparing action of forced carbohydrate and forced fat feeding prolongs survival. No definitive evidence is available to establish a favorable influence of carbohydrate and fat feeding on the progress of clinical renal disease as such, but the favorable influence of forced high-caloric nonprotein diets on the course of the uremic state has been observed previously.[4, 5, 6, 15, 17, 19] The purpose of this report is to add, to these observations, data demonstrating the value of nonprotein caloric supplements in acute and chronic renal failure.

Protein Sparing Effect of High Caloric Diet in a Normal Person. Although the protein-sparing action of carbohydrate and fat is a long-established dietary fact, Borst was the first to apply this principle rigorously in the treatment of uremia. Indeed, the possible reduction in endogenous protein catabolism

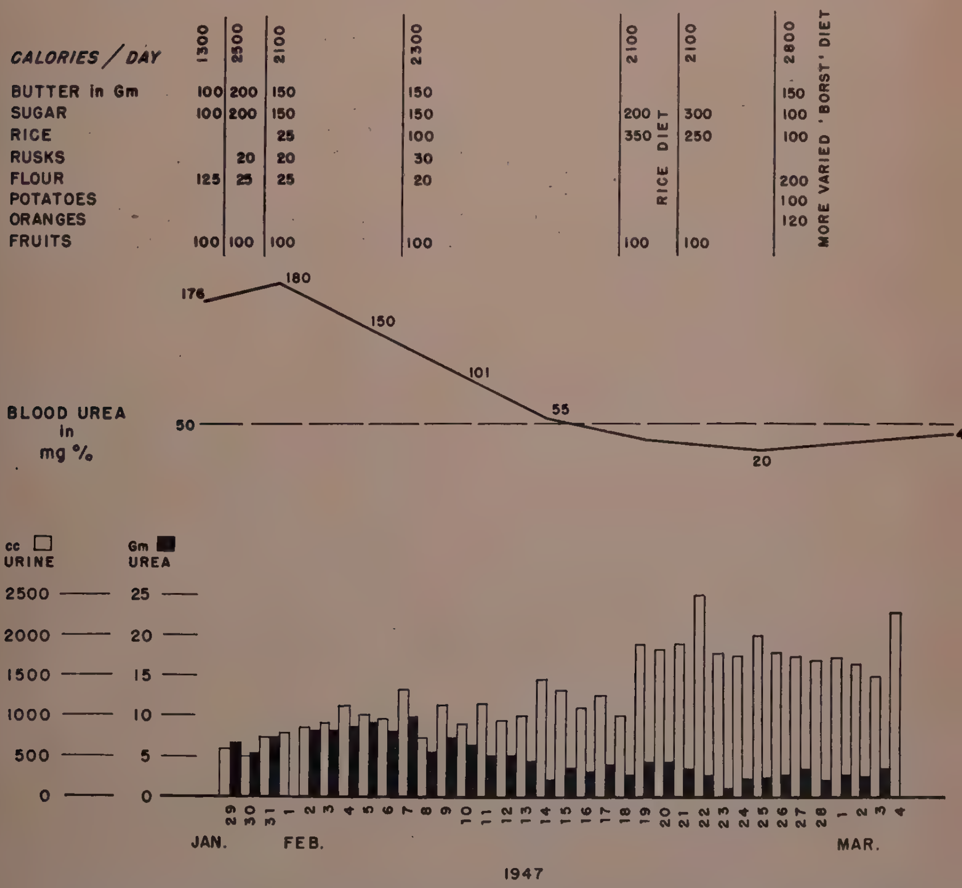

FIGURE 2. A man of 51 years of age with chronic glomerulonephritis, in uremia, was given a daily diet of 2100 to 2300 calories. His blood urea declined from 176 to 20 mg. per hundred ml. Kempner's and Borst's diets were equally effective in reducing urea production. The daily urea excretion was only 3 grams per day or less. (Am. J. Med., in press).

seems unbelievable. Studies based on this principle have been done in several patients with normal renal function.[4, 5, 6, 17, 18, 19]

FIGURE 1 illustrates the course of a physically normal 19-year-old girl, placed on a diet of butter and sugar. When the girl's caloric intake was covered with carbohydrate and fat, her endogenous protein catabolism decreased until only three grams of urea was excreted per 24 hours. This output corresponds to a protein breakdown of less than 20 grams daily. The 12 grams of urea excreted daily during fasting corresponds to the breakdown of 72 grams of protein. Why that much protein is catabolized, when large amounts of body fat are still available, is not known. Perhaps some day, a drug will be found to compel the utilization of body fat. Such anabolic effects as those of testosterone and methylandrostenediol deserve further study.

It can be calculated how high the blood urea of a patient on a high-caloric regime should be if all the urea excreted were retained in the body. Borst estimated that, after 23 days of complete uremia, the blood urea would have been 353 mg. per 100 ml., a level well below that at which death from uremia is to be expected. In contrast, the daily intake of 1.5–2 liters of milk would bring the blood urea to 577 mg. in six days, a terminal uremic level.

Protein-Sparing Effect of High-Caloric Diet in Patients with Uremia. An example of protein sparing in uremia is shown in FIGURE 2. This patient's urea clearance of 9–13 per cent of normal necessitated a severe azotemia before the diet was started. However, it permitted the excretion at normal blood-urea levels of two to three grams of urea, corresponding to the new rate of protein catabolism achieved by the diet. Associated with the relief of azotemia was a sense of greater well-being than he had had for a year.

Minimum Protein Intake. In view of the above, the uremic patient should never be given more protein than he is able to utilize. Such utilization depends on giving nonprotein calories. Without fail, proteins will be burned for calories, and the need for anabolic nitrogen will persist, unless energy requirements have been supplied.[22] Thus the protein requirement depends upon the caloric intake. This explains some of the controversy about Kempner's rice diet. Kempner[13] believes that the 20 grams of protein provided by his diet is adequate for nitrogen equilibrium. Peschel and Peschel,[25] Dole,[9] Corcoran, Taylor, and Page,[7] and Kolff[7, 18, 19] have confirmed this. If the patient does not take the *full* rice diet, however, or does not sufficiently cover his caloric requirements, he is forced to live on his body protein, and his nitrogen balance becomes negative.

Usefulness of the Diet in the Treatment of Uremia

Acute Uremia. Apart from its protein-sparing effect, the high-caloric diet has the advantage of preventing starvation ketosis, as was shown quantitatively by Gamble[11] and his group. Moreover, in its most rigid form, the regimen is practically free from potassium. It helps to keep potassium in the cells. It may even move potassium from the extracellular into the introcellular phase, as was demonstrated in a patient in anuria.[16]

The application of the diet in patients with acute uremia has been

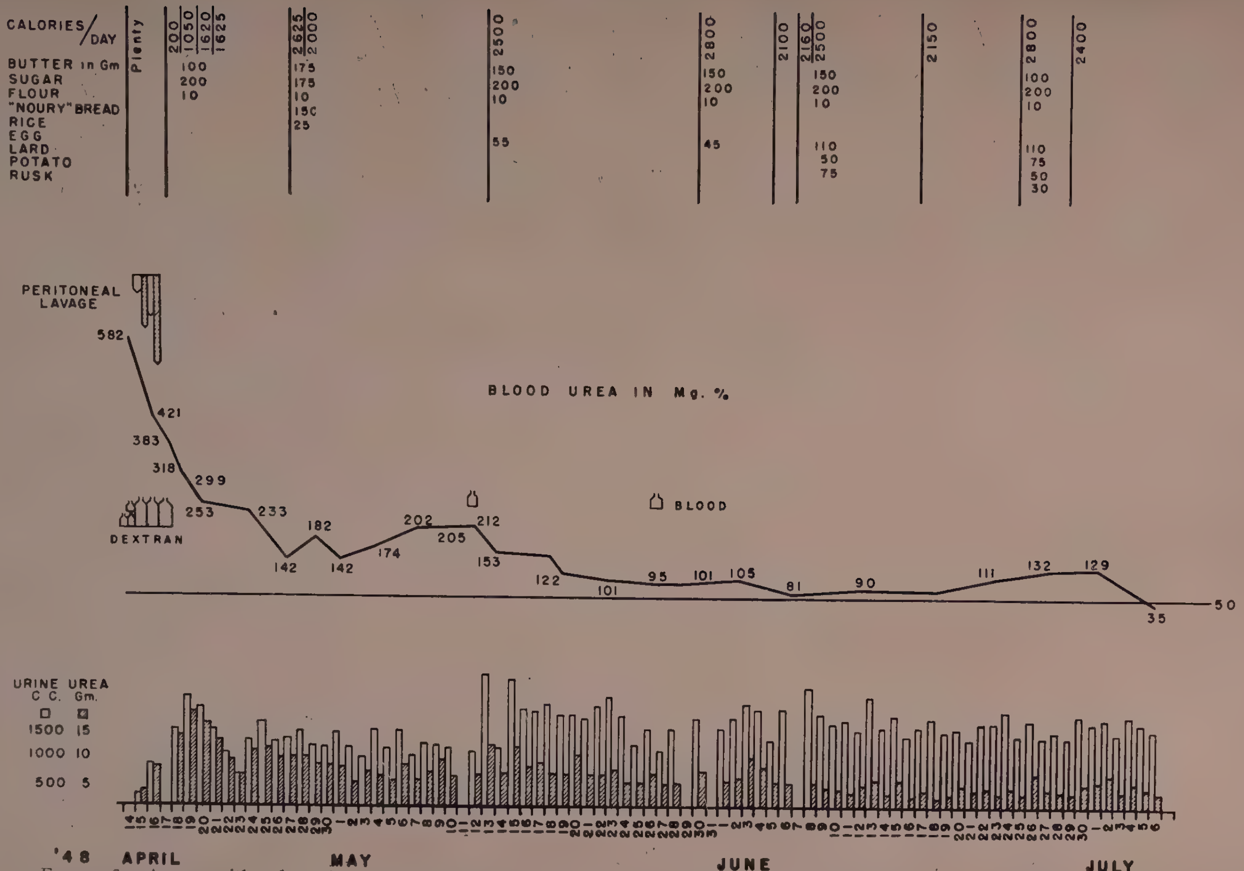

FIGURE 3. A man with polycystic kidneys and hypertension was first seen with a blood urea of 580 mg. per hundred ml. After peritoneal lavage, he was able to take a butter and sugar diet. When caloric intake was covered, 5 grams of Methionin, 2 eggs, and 50 grams of ordinary bread were allowed without noticeable increase in urea excretion.

Hypotension during dialysis was relieved by infusion of dextran (Macrodex) which, since it is a carbohydrate, seems preferable to other plasma substitutes in uremia. (Macrodex was supplied by Pharmacia in Sweden; and by Mr. Nathan Katz, Pharmacia Laboratories, Inc., New York, N. Y.)

demonstrated elsewhere.[17, 18] Severe infection, intoxication (bichloride of mercury), crushing injuries, major operations, *etc.* can obscure the effect of the diet because they cause protein destruction, both directly and indirectly. It is safe to assume that the principles which underlie the diet must prevail as soon as tissue destruction begins to subside. Consequently, the possible advantages of the diet should be made available from the start. Treatment with dialysis, artificial-kidney[14, 15] or peritoneal lavage[15, 20] may be required to bring the patient into a state which is amenable to dietotherapy.

Chronic Uremia. The application of the diet in chronic uremia is demonstrated in FIGURE 3. A man with polycystic kidney entered the hospital in semicomatose condition. His blood urea was 580 mg. per hundred ml. After one peritoneal lavage, he was sufficiently improved to take the diet. As his blood urea came down, some protein was allowed.

Despite grossly deficient kidney function, he went home with a normal blood urea. His daily excretion of urea was approximately five grams.

How Can the Adequacy of Dietary Control be Ascertained?

It is assumed that in normal subjects and in chronic uremia, urinary urea output is an adequate measure of the rate of protein breakdown. Consequently, in the absence of infection, intoxication, trauma, or hypermetabolism, urea excretion per 24 hours should not exceed about five grams, and is usually less. Sudden shifts of blood urea, or rapid changes in body weight should be taken into account. With these reservations, repeated determinations of the daily urea excretion are the best evidence of a proper dietary intake. If this is impractical, careful evaluation of the actual food consumed should be made, as is demonstrated in the following case (FIGURE 4). A 62-year-old man had two bouts of hematuria ten years ago. Twelve days before admission, he developed malaise, fever, proteinuria, and hematuria. The blood urea was 230 mg. per hundred ml. A 2400-calories, 20-grams-protein diet was prescribed and, since he was considered to be suffering from an exacerbation of chronic pyelonephritis, antibiotics were given. However, the blood urea continued to rise. A survey of his food trays showed that his intake was only 1000 calories daily. The importance of caloric intake was explained, and the diet was reduced to a volume he could eat, and supplemented with Lipomul-Oral. Within a few days, his blood urea started to fall and his general condition improved.

Treatment of Patients with Nephrotic Syndrome

The treatment of the nephrotic syndrome is still a problem in spite of ACTH, cortisone, nitrogen mustard, sodium restriction, and resins. High-protein diets are often prescribed with the aim of replacing urinary protein loss. Such increase in protein intake is often followed by proportional increases in proteinuria.

Use of high-caloric supplements as adjuncts to current methods for treatment of the nephrotic syndrome can be justified. The protein-sparing effect slows protein catabolism, and releases the protein intake in the diet for

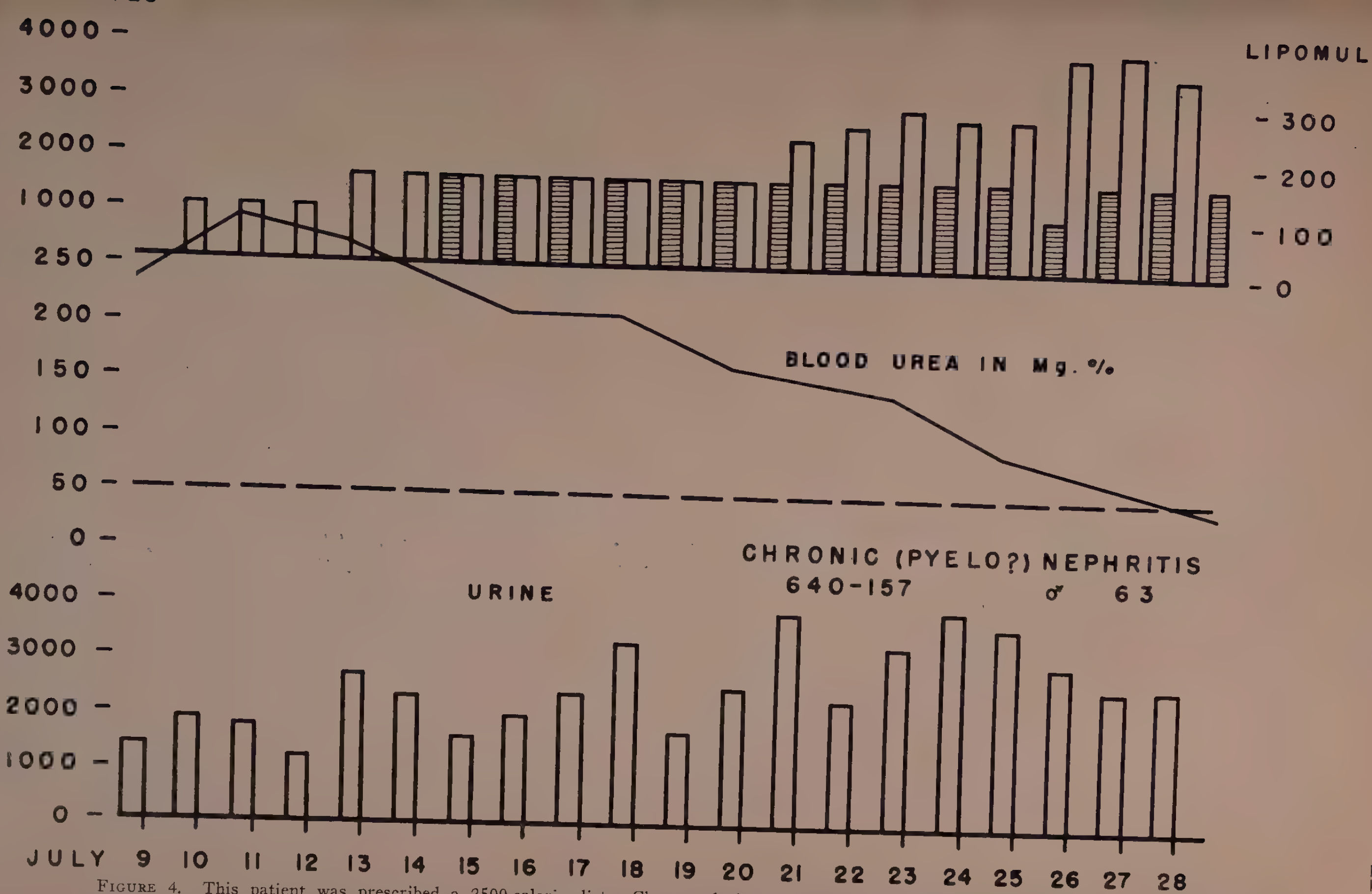

FIGURE 4. This patient was prescribed a 2500-calorie diet. Close analysis showed, however, that he hardly took 1000 calories of it. When intake was increased with 160 ml. of Lipomul-Oral (640 calories) daily, his blood urea began to fall. His caloric intake was increased as soon as he was able to take it, and his blood urea came down to a normal level.

anabolic needs and replacement of protein loss, while the supplements are sodium free. Results with this regimen in nephrotic children have been encouraging. Twiss[27] reported four cases, one of which is described briefly below.

A four-year-old boy had tonsillitis in August, 1947, followed by proteinuria and edema. Proteinuria persisted, and edema varied during the ensuing year of hospitalization until he was discharged in partial remission. He had several relapses and was never well in spite of treatment with a "salt-free" high-protein diet. On February 2, 1950, he was as ill as he had ever been, and was seen in the hospital in Kampen. Abdominal paracentesis was performed three times in 12 days, and more than 13 liters of fluid was removed. Body weight decreased during this time from 30.5 to 21.6 kg. He received a salt-free diet with butter and sugar supplements. His total daily intake was 1000–1400 calories and 40–45 grams of protein. Proteinuria remained constant at three to eight grams per 24 hours, but the edema disappeared completely. Within a short time, he turned from a seriously ill into a happily playing child. Blood hemoglobin increased from 68 to 103 per cent not withstanding his initial high serum lipid (cholesterol 800 mg. per hundred ml.). He tolerated the increased fat intake without apparent ill effects.

The treatment of adults with the nephrotic syndrome, especially in the presence of uremia, is much more difficult. A *status quo* is often all that can be obtained. Encouraging results were obtained in a patient with Kimmelstiel-Wilson syndrome, edema, and azotemia.

Administration of the Diets

Acute Uremia. Acute (anuric) uremia, or chronic uremia in an exacerbation, or chronic uremia, in what is prejudicially called the "terminal" stage, are treated in the same way as far as their caloric and protein management are concerned.

The amount of fluid output (including urine) will determine the desirable water intake. Butter and sugar are the most helpful ingredients in facilitating a high caloric intake. Butter can be served in the form of butterballs, chilled on ice or with sugar and some flour, as an emulsion flavored with coffee extract, or made up into a kind of pudding.

Large amounts of sugar can be given in fruit juices, jellies, and in diluted fruit flavors. Dextri-Maltose may be substituted for sucrose. Recently Lipomul-Oral* has become available as a high-caloric dietary supplement. This can be taken orally, and may have to be used as an alternative for the emulsion of Bull and Joekes[6] through stomach tube or jejunum fistula (extra sugar should be added).

When enteral feeding is impossible, one liter of 40 per cent glucose with insulin can be given by plastic catheter as a continuous drip into the right auricle. This provides 1600 calories in a small volume, and avoids multiple venous injuries.[8]

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* Lipomul-Oral, Upjohn, is an emulsion of vegetable oil plus 10 per cent sucrose in water with an emulsifier, and provides 4 calories per ml. It was provided through the courtesy of Dr. Earl L. Burbidge, Medical Director, The Upjohn Company, Kalamazoo, Michigan.

More recently, we have used invert sugar 20 per cent (Travert†) in water. One liter of Travert 20 per cent provides 800 calories. It was hoped that this solution might be tolerated when infused into the peripheral veins, but, after repeated infusion, thrombophlebitis developed in 4 of the 16 patients listed in TABLE 1. Alcohol 5 per cent, intravenously, was a useful supplement in some cases.

Chronic Uremia. Ambulatory patients with chronic uremia are given a 2000–3000-calorie diet, which contains about 20 grams of protein. More protein can be allowed if kidney function improves, or an anabolic phase supervenes. Thus, more protein is prescribed if blood urea falls below 50 mg. per hundred ml. or if a slight increase in protein intake is not followed by an increase in blood urea.

Borst described the following diet as useful in chronic uremia: butter, 100 g.; sugar, 100 g.; rice, 50 g.; flour, 125 g.; fruits, 200 g.; vegetable, 100 g.; cream, 200 g.; cocoa powder, 10 g.; and tea and coffee. This diet contains 2490 calories; nitrogen, 4 g.; potassium, 1280 mg. (33 meq.); and phosphorus, 470 mg. (15 meq.). All the ingredients of the rice diet can be used. There seems to be no reason why pepper, and other spices should be prohibited. Use of a special bread (Noury Bread*) containing 2.2 per cent protein, instead of the usual 7 per cent in most white bread, was very helpful. Patients can take a loaf along with them and are independent when eating in restaurants, picnics, *etc.* Practical suggestions for meals with foodstuffs available in the U.S. have been presented elsewhere.[17, 18]

If the caloric intake is inadequate in chronic renal insufficiency, it can then be increased by one of the ingredients discussed under acute uremia (butter soup, Lipomul-Oral, *etc.*).

Results

TABLE 1 summarizes observations with diet and supplements, notably Lipomul-Oral and Travert, during the last year. Most of these patients had a bad prognosis at the onset of their disease.

The following case reports exemplify two of these. A 57-year-old man with an acute exacerbation, of what was believed to be chronic nephritis, was admitted for treatment of progressive uremia. Blood pressure was 160/90 and blood urea 240 mg. per 100 ml. He had been given five blood transfusions in one week in another hospital prior to admission, but there was no history of transfusion reaction (FIGURE 5).

As he was unable to retain anything taken by mouth, he was given Travert 20 per cent in water, intravenously, for three days. Thereafter, he received 400 ml. Lipomul-Oral with water as a continuous intragastric drip. Marked oliguria persisted, but the blood urea stayed in almost the same level. After 17 days, vomiting made further intragastric feeding impossible. His blood urea was 273 mg. per 100 ml. From then on, one liter, Travert 20 per cent,

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† Travert 20 per cent inwater, contains 10 per cent glucose + 10 per cent fructose. It was provided by courtesy of Dr. Robert P. Herwick, Medical Director, Baxter Laboratory, Inc., Morton Grove, Illinois.

* Made by Nourypharma, Medical Division, Deventer, Holland. (Mr. Horbach.)

TABLE 1*

Diagnosis	*Number of patients*	*Lipomul-Oral*	*With success*	*20% Travert I. V.*	*With success*	*Thrombophlebitis*	*Butter soup*	*With success*	*Went home considerably improved or recovered*
Polycystic kidney with uremia	3	3	2	—	—	—	1	1	2
Chronic nephritis pyeloneph. t.b. nephritis plus psychosis	9	5	3	5	2	2	2	1	5
Uremias as complication of serious operation with or without peritonitis or fistulae	6	3	2	4	1	1	1	1	3
Carcinoma constricting ureters	2	1	0	2	0	1	—	—	0
Lupus E. plus edema	1	1	0	—	—	—	—	—	0
Kimmelstiel-Wilson plus edema	4	2	1	2	1	—	1	0	2
Cancer of prostate stones hydronephrosis	4	4	3	1	1	—	—	—	3
Transfusion reactions plus complications, shock pancreatitis	4	2	1	3	2	—	1	1	1
Total	33	21	12	17	7	4	6	4	16

* Results of treatment of 33 uremic patients with various high-caloric regimes. Twenty-one used Lipomul-Oral, 17 were given 20 per cent Travert, 6 butter-sugar emulsion.

The columns headed "with success" mean: willing and able to take the particular substance for some time with a fall in blood urea, or reduction in urea formation, evident prolongation of life, or clinical improvement. One patient, for example, was successfully treated by alternating Lipomul-Oral and Travert. He improved, but later died from a myocardial infarct, and therefore is not included in the last column.

Patients needing Travert are usually the ones in whom Lipomul-Oral has been ineffective or impractical. They are sometimes able to take it after treatment with Travert.

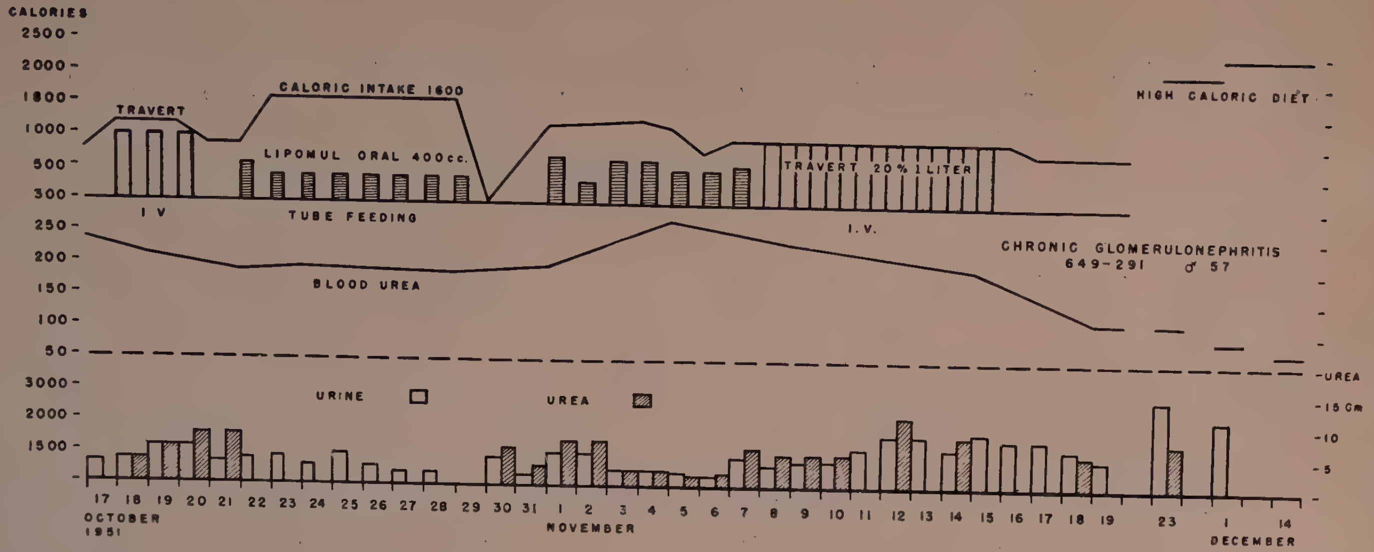

FIGURE 5. This patient with chronic glomerulonephritis was unable to retain any food given by mouth. A period of severe oliguria for one month had to be bridged with artificial feeding. Lipomul-Oral per continuous gastric drip and Travert 20 per cent in water, intravenously, supported his caloric intake and the blood urea was maintained between 200 and 300 mg. per hundred ml.

Finally, his diuresis increased and he was able to take a 2400 calorie diet, whereupon his blood urea fell to 90 and 70.

intravenously, provided 800 calories per day, while water and electrolyte loss by vomiting was compensated with 1.5 liters of three per cent glucose, with varying amounts of salts, per day. Thirty days after the onset of artificial feeding, he was finally able to take 800 calories orally.

As soon as possible, his intake was increased to 2400 calories per day, including 20 grams of protein. Butter soup and whiskey were used to boost his caloric intake. He was discharged on the fifty-fifth hospital day with a blood urea of 78 mg. per hundred ml.

One month later, he was increasing his activity, and maintaining a caloric intake of 2500 calories. His blood urea was 72 mg., and he left for a vacation in Florida.

It must be admitted that the actual goal, a high caloric intake, was not reached until the end of the period, but such compromises have to be made frequently. It is noteworthy that his diuresis suddenly increased on November 12, and again on November 23. These unpredictable changes, inexplicable but fortunate, offer encouragement to physicians treating patients seemingly moribund from chronic renal insufficiency.

A 47-year-old man with large polycystic kidneys entered the hospital complaining of headache and dizziness. Blood pressure was 140/94 mm. Hg, and blood urea 270 mg. per 100 ml. (FIGURE 6). He was placed on a high-caloric low-protein diet, with a supplement of 180 ml. Lipomul-Oral (720 cal.). In a week he had adjusted himself to the diet and was discharged with a blood urea of 192. One month later, after continuing the diet and the Lipomul-Oral at home, his blood urea had come down to 60.

He continued on a 2000–2500-calorie diet and took Lipomul-Oral for 5½ months. His blood urea remained between 72 and 90. He said that he felt better than he had during the last few years.

Complications of the Diet. The two complications inherent in the use of these diets are potassium depletion and avitaminosis. The former is most likely to develop in patients who are isosthenuric and polyuric, and it can be avoided by appropriate supplements of potassium salts.[16]

Multiple vitamin deficiencies may develop rapidly when caloric intake is suddenly increased with purified food substitutes. Vitamin supplements should be provided from the outset.

Summary

Experiments in animals indicate that protein deleteriously affects the course of uremia and, possibly, of renal disease. Uremia in nephrectomized animals is favorably influenced by high-caloric nonprotein feeding, which seems to act by decreasing protein catabolism.

Protein-sparing effects of high-caloric feeding are demonstrable in normal subjects and in uremic patients. In the cases cited, decreased endogenous protein metabolism is evidenced by rates of urinary urea output of two to five grams daily.

Catabolic effects of trauma and infection counteract the benefits of high-caloric nonprotein feeding. In spite of this, the diet should be instituted from

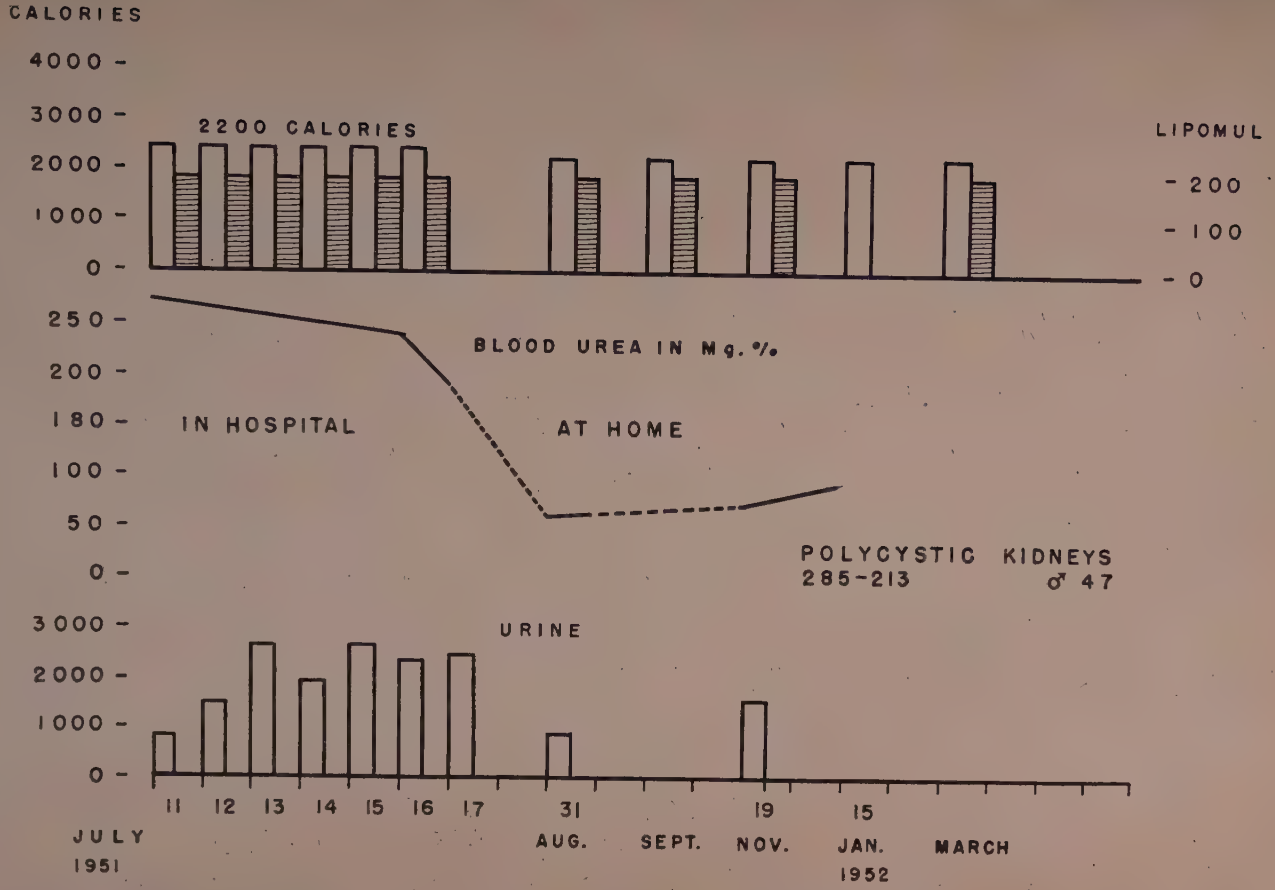

FIGURE 6. A man with polycystic kidneys and uremia had been in extremely poor health the last year. He was given a 2200-calorie low-protein diet, including 1600 ml. of Lipomul-Oral. His blood urea came down to between 60 to 90 mg. per hundred ml., and he improved clinically. At present, 10 months after the beginning of the graph, he is still taking the diet and feeling reasonably well.

the outset of treatment, in the expectation that the complications will be brought under control.

In chronic uremia, adequacy of dietary control usually can be estimated from urine-urea output. When nonprotein calories are adequately maintained, protein intake can be safely reduced to 20 grams daily for long periods.

The favorable effect of protein-sparing in the nephrotic syndrome is illustrated by a description of one of several cases so treated.

High-caloric alimentation is facilitated by use of supplements such as Lipomul-Oral and Travert 20 per cent.

Complications of such diets (potassium deficiency, sudden onset of avitaminosis) should be avoided.

A review of 33 patients treated according to these principles, some of whom were desperately ill when treatment began, demonstrates the value of high-caloric, nonprotein alimentation in acute and chronic uremia.

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IMPORTANCE OF CALORIES IN THE GROWTH OF CHILDREN

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Growth is characterized by activity and change. In man, the attainment of structural and functional maturity is accompanied by a series of anatomic and physiologic changes during the transitions from prenatal life, infancy, and childhood to adulthood. The growth mechanism itself is little understood. Experience, however, has demonstrated that, if the growth impulse is to proceed unimpeded, there must be furnished in the diet a liberal supply of all those nutriments that are essential for the construction of new tissues and for continuous maintenance and function of all body activities. In addition, the food supply must furnish sufficient energy to provide for a reasonable reserve, which may be drawn upon in times of unusual stress or augmented needs.

The experiences in one epoch of the life cycle may be carried over into another, and thereby modify biochemical individuality and alter metabolic requirements during succeeding stages of growth and maturity. The interinvolvement of these influences is demonstrated for women in FIGURE 1. Shortages in the energy supplied by a diet must be met, even at the expense or sacrifice of body tissues which in turn may retard, frustrate, or thwart the growth impulse in its persistent drive or struggle towards maturity of structure and function of the body.

In children, there is a delicate balance between the dynamics of energy and protein metabolism during protoplasmic growth. Biochemical individuality may be modified by both rate and quality of growth, and it may thereby influence the metabolic needs at a given time. Visible growth (increase in body size) may be determined directly by observing progressive changes in body dimensions and weight at consecutive intervals of time with increasing age. Invisible growth may be measured indirectly by the study of absorption from food and storage in the body of structural and functional constituents, by basal metabolic rate determinations, and by roentgenographic recordings. It is obvious that observations of invisible growth contribute to a better understanding of the quality and quantity of the chemical increments necessary for all aspects of growth.

The data used for this discussion were taken from the results of a comprehensive investigation of nutrition and chemical growth in childhood[1] over the past twenty years. The subjects were carefully selected as active healthy individuals with satisfactory nutritional and growth records, and well-stocked body stores. None were obese. They had good appetites; their skeletal ages were comparable to, or above chronological ages, and the children were well-adjusted and happy during the studies. The investigation was carried on with the children living in a cottage with the necessary staff, and interference with normal activities was minimal. Diets were composed of the same 22 common foods adjusted to the appetites of the individuals. Daily fluctuations in hunger demands were met by flexible intakes of sugar. In general, protein intakes were increased by provision of increased energy intakes, and the percentages of total calories provided by proteins of high biological value were fairly constant (14 to 16 per cent of the physiological fuel value). On the average, the diets contained protein, fat, and carbohydrate in amounts which were 18, 24, and 58 per cent, respectively, of their combined weight.

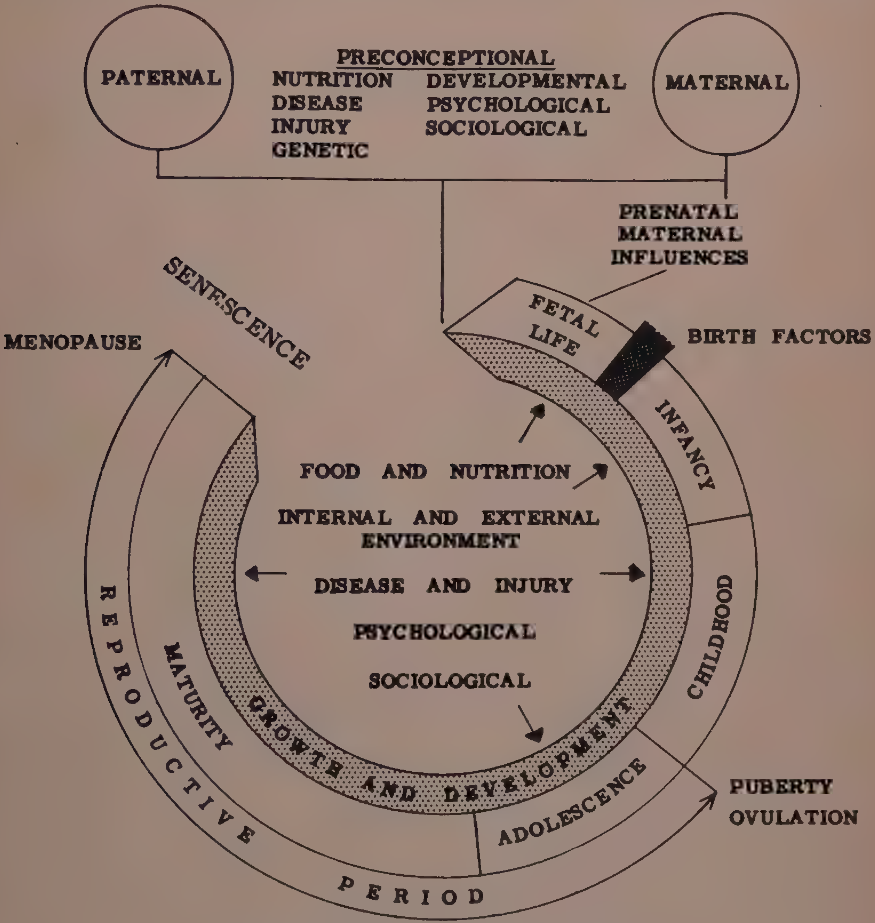

Figure 1. Epochs in the life cycle of woman.

The biological evaluation of dietary adequacy, by relating energy intake to weight increase and to nitrogen storage, emphasizes that neither appetite nor any of the known standards can be relied upon to assure ingestion of quantities of a good, mixed diet which will provide sufficient calories for satisfactory weight gains of individual children. A short time after the balance studies were started, the analytical results demonstrated that for some children the diets which satisfied appetite were not providing sufficient calories to permit satisfactory nitrogen storage and weight gain. The intervals of insufficient calorie intake were too short to produce significant losses of body tissue, and increased food intakes were followed by rapid weight gains.

If the potentialities of the growth impulse are to be realized in full measure, a diet should provide protein with a satisfactory mixture of amino acids for fabrication of protoplasmic tissue, minerals and vitamins for construction of body tissue and maintenance of body function, and adequate calories from fat and carbohydrate. The results of determinations of energy and of nitrogen utilization and body-weight gain reflect the influence of factors that modified the changes in structure and function which were taking place concurrently in the children's bodies. If the growth impulse is a constant force, the "change in size" which constitutes visible growth seldom manifests constancy. The vicissitudes of existence are known to present variable requirements for repair which are superimposed upon those for maintenance and growth. Growth may be limited by "conditioning," resulting from the body's adaptation to an insufficient or improper diet over a considerable period of time. Increases in body mass may consist largely of water and adipose tissue instead of protoplasmic tissue.

Among the 29 children at different age levels studied during 593 five-day balance periods, retention of nitrogen for tissue construction was depressed when the calorie intake level was insufficient. Sometimes, the rate of increase in body weight exceeded the accretion of nitrogen by far. At other times, there was no gain in body weight for a time, although nitrogen was being retained. To illustrate, during seven consecutive months Barbara showed varying gains in weight and retentions of nitrogen, while her intake of calories ranged between 1471 and 1532 per day. Per kilogram of body weight, Barbara's daily intake of calories declined consistently during the seven months from 92 to 78, and her protein intake dropped from 3.6 to 3.1 grams/kg./day. During the first month of study, Herbert was losing weight and nitrogen on an intake of 1514 calories per day, 74 per kilogram of body weight. With his food intake increased to supply 1747 calories, during the next month, the boy gained weight and maintained equilibrium with respect to nitrogen. The third month, 1821 calories per day (86 per kilogram of body weight) brought about storage of nitrogen and weight gain, but the same intake during the following month was accompanied by greater nitrogen retention, with a *loss* of body weight. For two months, nitrogen retention continued, with slight weight gains. The final month of study showed little change in nitrogen retention, but body weight increased very rapidly.

Although changes in body mass may not be a true measure of chemical growth, it seems significant that in healthy, well-nourished children as few as 10 calories per kilogram of body weight may determine success or failure in making satisfactory growth progress. Ill and less fortunate children, with poorly nourished bodies, vary more widely in their calorie and protein needs, and, for them, a small deficit in calorie intake may have far-reaching detrimental effects, not only with respect to body weight, but also upon tissue formation and physiological function. Mineral metabolism and skeletal maturation may also be influenced by such circumstances.

The criterion of adequate energy intake for a child at any time must be based upon growth, rather than upon compliance with dietary allowances for population groups, or upon standards developed without sufficient consideration of nutritional status, varying activity, and progress of growth. It is important to interpret individual calorie needs in terms of a child's own growth, for individual requirements may vary among those of the same age and size. For the children who were subjects of the study,[1] in most instances, twice the basal metabolism per 24 hours exceeded the determined physiologic fuel value of the food intake, and, for the majority of the children, it exceeded the heat of combustion of the intake. It would appear that an allowance of foods, providing calories in quantities 50 to 100 per cent above the basal metabolism per 24 hours, depending upon activity, would meet the usual requirements of metabolism and activity for most healthy growing children, whether the calorie intake was determined (or calculated) on the basis of either heat of combustion or of physiological fuel value.

With the search for better understanding of the body's requirements for nutriments other than calories, less attention has been focussed upon the problem of adequacy with respect to energy, especially in children; yet without sufficient calories, utilization of other substances may be impaired, and growth inhibited. The validity of the allowances recommended by the Food and Nutrition Board of the National Research Council as a guide in planning adequate intakes of calories for groups of children is supported by our findings. The Board emphasizes that the recommended calorie allowances be regarded as subject to modifications of plus or minus 15 to 20 per cent according to conditions. Objections to the levels advocated as being unnecessarily high are not substantiated with respect to energy intake by the results of our investigations. All of the children received diets providing calories within ±20 per cent of the recommendations on the basis of body weight. The food intakes provided average daily energy intakes, which were 95 to 113 per cent of the allowances recommended for age. Over the seven months, the daily energy intakes per kilogram of body weight ranged from 89 to 100 per cent of those recommended. The children, with the least-satisfactory initial weight gains, and larger increases in calorie intake, voluntarily maintained higher daily intakes than at the start of the study. All of the children decreased their levels of intake per kilogram of body weight during the latter months of the study, providing a striking demonstration of the effectiveness of an adequate diet composed of wholesome common foods. Differences in type and speed of growth were observed with increases of 4 to 11 calories per kilogram of body weight per day. Weight gains were recorded for children who had showed slight losses during the preceding 30 days. The data suggest that in children's bodies, given the opportunity, a period of inadequate calorie intake may be compensated for by high consumption, followed by a lowering to normal demand levels.

The results demonstrate that a difference in intake of only a few calories per kilogram of body weight per day may mean nutritive success or failure, even with a dietary excellent with respect to all other essential nutriments. Nutritive failure might consist of "conditioning" to a diet unfavorable for growth, and might influence health and development throughout subsequent epochs in life. Such "conditioning" may occur without producing demonstrable evidence of malnutrition. However, lack of only a few calories per day for even a few weeks might be followed by permanent and irreparable consequences in undernourished or malnourished children.

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INTERRELATIONSHIPS OF FOODSTUFFS

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What I have to say seems to me of doubtful relevance to the subject of this monograph, since I have had no direct experience with oral fat emulsions. However, Dr. Stare was sufficiently intrigued by an article I wrote for the Yale Journal of Biology and Medicine to ask me to give a repeat performance. I shall not comply with his request literally because the article was too long, and not intended for technical treatment. It was a plea for a better integrated view of metabolism—an argument against the purely categorical approach and the segregation of ideas according to techniques. In an earlier approach to the problem I suggested that a distinction be drawn between *energy metabolism* (that is, the supply and utilization of foodstuffs for the production of energy) and *operative metabolism* (the processes that give this energy direction, permitting it to be used for differentiated purposes). This distinction will be maintained here.

The three foodstuffs (fat, carbohydrate, and protein) may all serve as fuel, but not indifferently. Each has an operative as well as an energy-producing function. A small amount of carbohydrate is essential for purposes that will be considered later. If adequate amounts of it are not continuously supplied in the food, it must be manufactured from protein—an inefficient and wasteful process.

Fat is an ideal fuel because its caloric value is so great in proportion to its mass. It is formed freely in the body from carbohydrate. So far as its fuel value is concerned, it is an indifferent substance. Nevertheless, if an animal is given a diet devoid of fat, but containing enough carbohydrate to supply its caloric needs, it will lose weight and ultimately die with characteristic lesions, including a fatty liver and degeneration of the kidneys. The origin of these disorders appears to be the inability of animals to synthesize certain essential fatty acids having 18 or more carbons and more than one unsaturated bond. The principle acids of this group are:

Linoleic acid	18 carbons	2 unsaturated bonds
Linolenic acid	18 carbons	3 unsaturated bonds
Arachidonic acid	20 carbons	4 unsaturated bonds

It seems probable that natural fats contain other essential components, the nature of which has not yet been elucidated.

Fats proper (triglycerides) are found in adipose tissue. They are both found in and utilized by the cells of the liver, but they do not appear to be normal constituents of most other tissue cells. Nevertheless, fatty acids are burned by tissue cells. In these cells, fatty acids occur in cholesterol esters and phospholipids. The tissue cells presumably burn the fatty acids of the phospholipids, which may serve as vehicles for these fatty acids and as instruments that facilitate their oxidation. A characteristic phosphatide, lecithin, has the general composition of a fat, except that one of the fatty acids is replaced by a phosphoric acid and the methylated nitrogen-containing compound, choline (see FIGURE 1). Of the two fatty acids, one is usually unsaturated. To provide these unsaturated acids, the essential fatty acids seem to be required. The ordinary saturated fatty acid is preferentially used for fuel, while the unsaturated members, together with the other components of the compound are conserved with great care. The choline of lecithin, another essential dietary constituent, must be supplied pre-formed in the food, or else methionine must be given to provide the active methyl group for its formation. There are other phosphatides, distinguished from lecithin by the possession of compounds other than choline, among which serine and inositol have been identified. The latter is also an essential dietary constituent. The analogy between these compounds (which, together with phosphorus, form the phosphatides which seem to facilitate the transport and oxidation of fatty acids) and water-soluble vitamins (that participate with phosphate in the formation of enzymes) is intriguing.

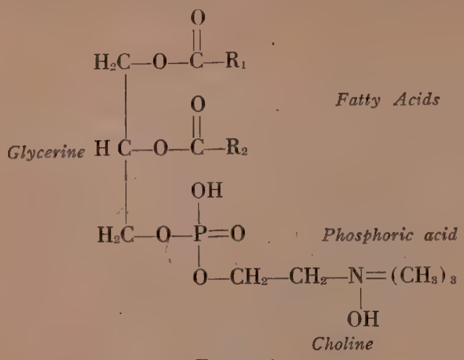


FIGURE 1

Since protein contains nitrogen, it can not be replaced by either carbohydrate or fat, though it can replace both these other foodstuffs. It is not, however, an efficient fuel because it cannot be completely oxidized in the body. Furthermore, it serves operative functions of such importance that it is not economical to waste it for fuel alone. Proteins are complex combinations of amino acids. Of the 23 amino acids generally recognized, 10 have been termed essential, not because they are more indispensible than the others, but because they can not be synthesized in the body. Therefore, life

TABLE 1

ARGININE
CITRULLINE
LYSINE
HYDROXYLLYSINE
HISTIDINE
PHENYLALANINE
TYROSINE
TRYPTOPHANE
PROLINE
HYDROXYPROLINE
GLYCINE
ALANINE
SERINE
THREONINE
VALINE
LEUCINE
ISOLEUCINE
NORLEUCINE
METHIONINE
CYSTINE
GLUTAMIC ACID
HYDROXYGLUTAMIC ACID
ASPARTIC ACID

can not be supported if they are not supplied in the diet in adequate quantities and proper proportions. Rose has shown that if optimum quantities of each of the essential amino acids are given, the remainder of the nitrogen requirements, presumably for the formation of other amino acids, can be supplied in almost any form. Under these circumstances, even ammonia and urea, usually regarded as waste products, can apparently be utilized for synthetic purposes. The amino acids generally recognized are listed in TABLE 1, with the ten essential ones capitalized. Most of the essential acids occur in varying proportions and innumerable permutations and combinations in

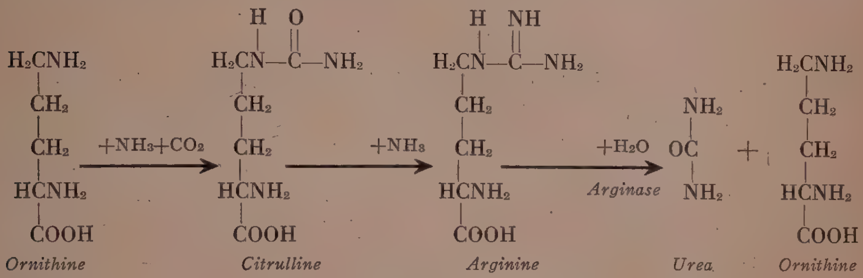


FIGURE 2

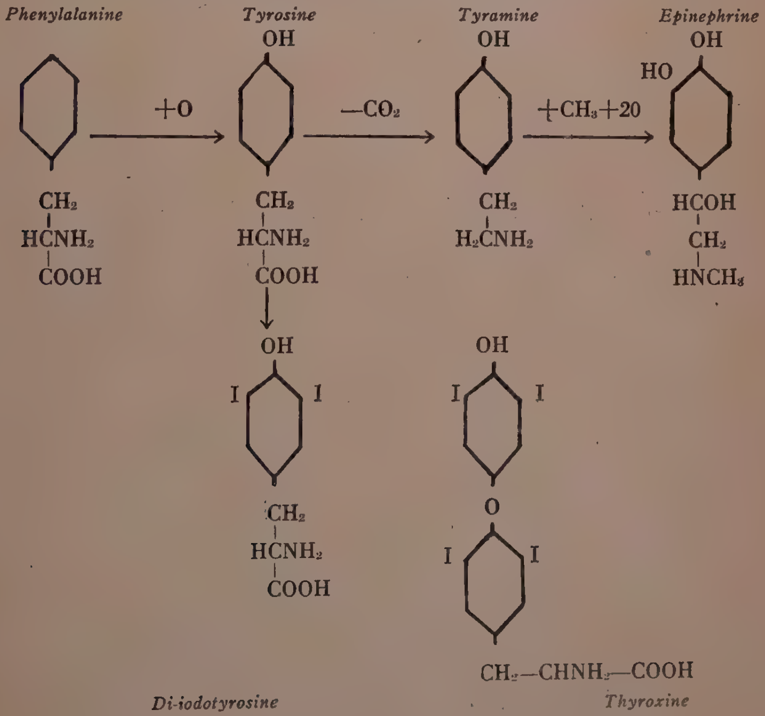


FIGURE 3

proteins. Some are known to participate in certain specific processes. Arginine, which can apparently be synthesized to a limited extent, is the chief vehicle by which ammonia is conveyed to the liver for the formation of urea. Arginine also contributes its amidine group to form creatine. FIGURE 2.

Phenylalanine can be used to form tyrosine, if the latter is not included in the diet, but no amount of tyrosine can be substituted for phenylalanine, which must, therefore, have certain independent functions. From tyrosine both thyroxine and epinephrine appear to be elaborated (FIGURE 3).

Methionine contributes fractions of itself for a variety of purposes (FIGURE 4). The methyl group at the top provides active methyl groups for both of the essential substances, choline and creatine. The sulfur is used for the formation of cystine, cysteine, and secondarily glutathione and other sulfhydryl compounds, with the aid of another amino acid, serine, which can be synthesized in the body.

In addition to the replacement of protein in the body, therefore, proteins must supply amino acids for specific purposes. This entails the continuous degradation of a certain amount of protein. The capacity of a well-fed individual to store protein is extremely limited, although this limitation may have been exaggerated. The greater part of any excess of protein is burned in spite of its high value. In the process of combustion, the nitrogen is broken off as ammonia which is excreted as such or as urea. The remainder is converted to materials that can be oxidized through the channels of either carbohydrate or fat.

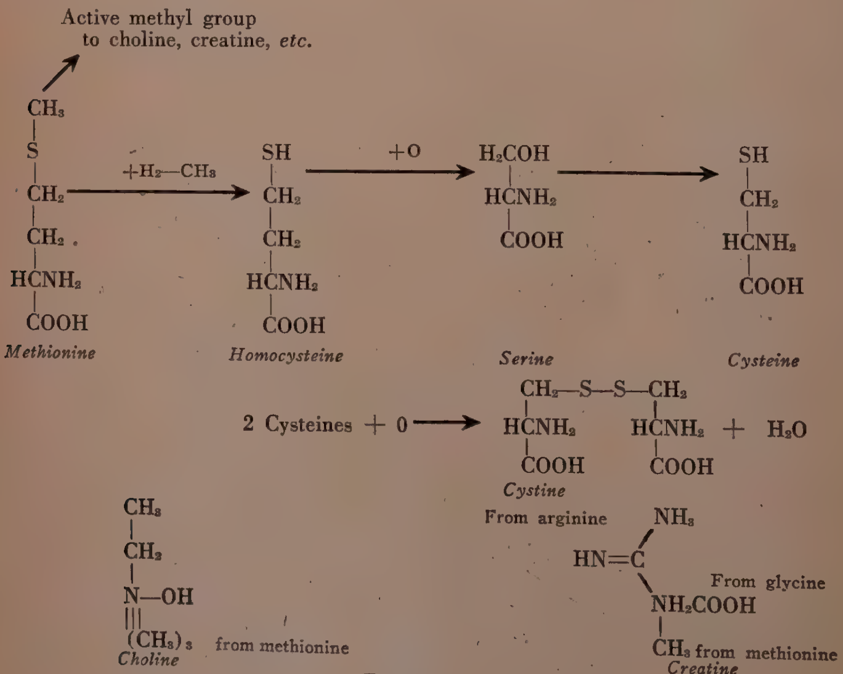
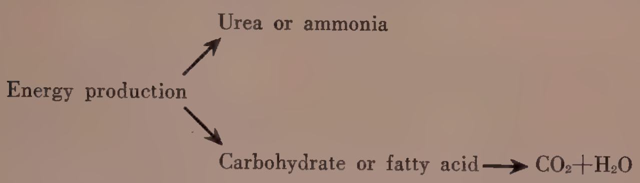
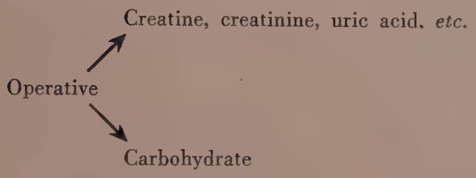


FIGURE 4

The end-products of the energy-producing metabolism of protein are, therefore, CO_2, H_2O and urea or ammonia (sulfate may be neglected for our purposes). In the urine, in addition to urea and ammonia, less completely metabolized nitrogen-containing compounds, such as creatinine and uric acid, are found. When the protein in the diet is varied, the excretion of urea plus ammonia varies accordingly, but that of other nitrogenous substances remains almost unchanged. These substances, of which creatinine is an example, are products of operative metabolism which must continue uninterrupted to maintain vital activities. Urea and ammonia, since they are products of energy-producing processes, vary with the nature and quantity of food available. Even the energy-producing function of protein is not entirely independent of operative needs. Since protein is the only source of carbohydrate when the latter is not provided in the food, it must, under these circumstances, take over the operative offices of carbohydrate. Proteins are not mere structural components of tissues, but extremely active agents, more than any others responsible for the differentiation and specialization of vital activities. For example, they form the cores of enzyme systems.





The composition of a large number of vitamins is now known, while only some of their functions have been elucidated. It is time they were called by their proper names, not distinguished only by letters and numbers. They participate in the reactions constituting the operative metabolism. Many, especially of the B-vitamin group, serve as components of enzyme systems.

Enzymes have proved to be complexes that can be isolated and identified, and which participate in the chemical reactions which they facilitate. The reaction of an isolated enzyme is, like other chemical equilibrium reactions, reversible. In its native habitat, however, the action of an enzyme is usually oriented, proceeding predominantly in one direction because it is linked with other, similar reactions in an enzyme system. The speed and direction of an enzymatic process is determined by the relative activity of the various components of the enzyme system, as well as by the quantities of materials provided. In addition, provision is made through the linked reactions of an enzyme system to restore to each enzyme the activity which it loses in the course of the single reaction it implements. Biological reactions are seldom spontaneously reversible. If, in the course of a series of reactions, the original reagents are reconstituted, it is usually by a cyclical or circuitous route.

The liver can both take up and give off glucose, but the simple equilibrium equation, glucose $\rightleftharpoons$ glycogen, is an altogether inadequate representation of the facts, which are shown in condensed form in FIGURE 5. Glucose enters and leaves cells, not by simple diffusion, but by an active chemical reaction, probably implemented by the enzyme, glucosekinase and adenosinetriphosphate, by which it is converted to glucose-6-phosphate. This compound is then converted to glycogen by a reversible series of reactions. From the liver, glucose can escape again, but not by reversal of the glucosekinase reaction, its exit being effected by means of a separate enzyme, phosphatase. The muscles do not yield glucose to the blood because they lack the proper phosphatase. The glucosekinase reaction appears to be influenced by insulin. From glucose-6-phosphate in both liver and muscle, but especially in the latter, the sugar passes to combustion through the intermediary product, fructose-6-phosphate. If combustion is accelerated, glucose-6-phosphate is diverted from glycogen and blood glucose. In the liver, fructose-6-phosphate can be formed directly from fructose which gains access to the cells by the aid of a specific hexokinase, fructosekinase, discovered by Cori, which is not influenced by insulin. Consequently, fructose is removed from the blood of a diabetic person or animal with the same facility as from the blood of a nondiabetic subject. Furthermore, fructose can not return to the blood stream from the liver because there is no phosphatase that acts on fructose-6-phos-

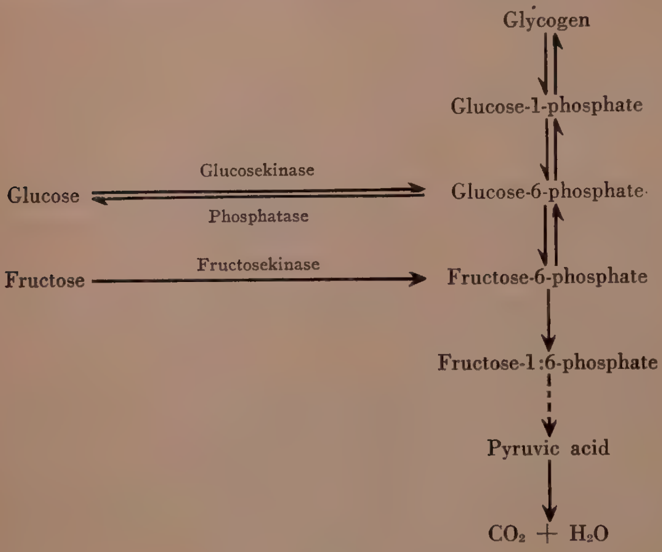


FIGURE 5

phate. Its only mode of escape is by conversion to glucose-6-phosphate by reversal of the normal sequence of reactions, whence it can be returned to the blood as glucose. This has raised hopes that fructose might be useful in the treatment of diabetic acidosis. There is some evidence that it may be utilized better than glucose by diabetics, and especially that it may induce less hyperglycemia. This can only mean that the reaction, from fructose downwards towards oxidation, is more rapid and vigorous than the reversal of the reaction upwards towards glucose-6-phosphate. There is still some doubt whether fructose can be used freely in severe diabetes, such as diabetic acidosis. Its utility will certainly be limited for two reasons. There is great doubt whether muscles possess fructosekinase. If they do not, the sugar will not enter the muscles until it has been converted to glucose by the liver. In the second place, it must be given parenterally because the intestines convert the major portion of oral fructose to glucose. The problem is presented here, not so much for its application to the treatment of diabetic acidosis, intriguing as that may be, but for the light it throws on the peculiar orientation of enzyme systems and the possibility, now commanding attention, that some metabolic blocks may be circumvented or by-passed by the introduction of appropriate intermediary products at strategic points.

When glycogen is burned, it does not pass through glucose as an intermediary, but through glucose phosphates and fructose phosphates to pyruvic acid. In FIGURE 6, most of the intermediate steps, including those by which the 6-carbon sugars are split into 3-carbon groups to which pyruvic acid belongs, have been omitted. From pyruvic acid, several alternate paths present themselves. The incomplete oxidation to lactic acid in the absence of a sufficient supply of oxygen will be neglected despite its importance.

Sustained activity with carbohydrate as fuel requires oxygen and from pyruvate onwards proceeds through the Krebs cycle, which has been drawn in circular form to emphasize its cyclical character (FIGURE 6). It is pictured as proceeding clockwise from the 12 o'clock position at the top, where oxaloacetic acid, a 4-carbon group, comes up on the wheel to combine with pyruvic acid, a 3-carbon group. The numerous compounds involved in the cycle will not be considered in detail. It will be noted first that by the addition of a molecule of CO_2, oxaloacetic acid can be formed from pyruvic acid.

$$\underset{\textit{Pyruvic acid}}{CH_3COCOOH} + CO_2 \longrightarrow \underset{\textit{Oxaloacetic acid}}{HOOCCOCH_2COOH}$$

$$CH_3COCOOH + 5\ O \longrightarrow 3\ CO_2 + 2\ H_2O$$

Since oxaloacetic acid is the beginning and end of the cycle, it follows that the cycle can be primed or renewed at any time from pyruvic acid by this reaction. To oxidize pyruvic acid completely requires five atoms of oxygen, producing three molecules of CO_2 and two of water. Let us assume, then, that oxaloacetic acid has been formed by combination of pyruvic acid and CO_2, and that another pyruvic acid has been fed to the oxaloacetic acid to start the cycle on its way. At the very beginning of the cycle, one atom of oxygen is taken up and a CO_2 given off to form the next member of the cycle, the 6-carbon cisaconitic acid. If attention is paid entirely to the oxygens that enter, and to the CO_2's and H_2O's discharged as the wheel turns, it will be seen that, at the completion of the cycle, the pyruvic acid fed to the oxaloacetic acid has been oxidized precisely and completely, leaving the

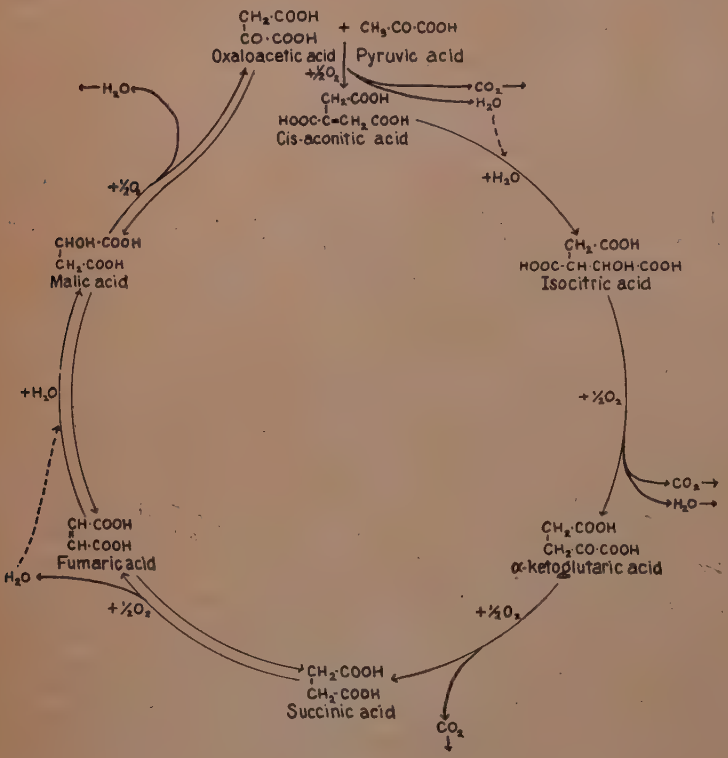
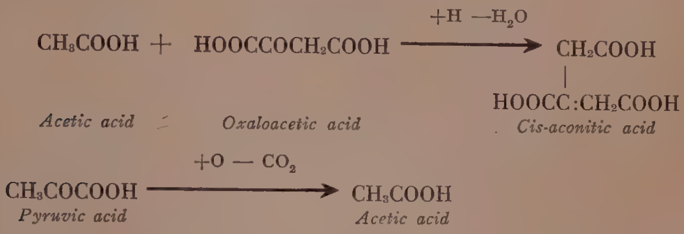


FIGURE 6

original compound, oxaloacetic acid, intact and ready to start another cycle to burn another pyruvic acid. The cycle can, therefore, be regarded as a device for the combustion of pyruvic acid, a burner. Although the energy to run this device is derived from the combustion of the pyruvic acid, this is not the actual machinery of muscular activity, but the power plant. The contraction of muscle, towards which this energy is directed, probably resides in less-well comprehended reactions in which the proteins of the muscles are concerned. From time to time, a small amount of pyruvic acid will be required to replace oxaloacetic acid which may have been inadvertently consumed, but otherwise the device is self-perpetuating.

Other fuel might be burned equally well in the Krebs combustion device. Suppose the 2-carbon acetic acid were added to oxaloacetic acid.

By the addition of an atom of hydrogen and loss of a molecule of water, it could form cisaconitic acid, the next acid in the cycle, thus starting the round, at the end of which the acetic acid would have been burned, leaving oxaloacetic acid again. Although this particular reaction is hypothetical, it has been established that 2-carbon compounds are produced from carbohydrate and oxidized, presumably over the Krebs cycle, and that acetic acid can be consumed in the same cycle. These 2-carbon groups and acetic acid might be suitable fuel for the combustion device, but quite incapable of replacing oxaloacetic acid to keep up the machinery. There is experimental work that suggests that pyruvic acid is essential for the production of oxaloacetic acid.



$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Oxaloacetic acid}}{HOOCCOCH_2COOH} \xrightarrow{+H\ -H_2O} \underset{\text{Cis-aconitic acid}}{\begin{array}{c} CH_2COOH \\ | \\ HOOCC{:}CH_2COOH \end{array}}$$

$$\underset{\text{Pyruvic acid}}{CH_3COCOOH} \xrightarrow{+O\ -\ CO_2} \underset{\text{Acetic acid}}{CH_3COOH}$$

Fats and fatty acids contain very little oxygen in proportion to carbon and hydrogen and yield in their combustion a large number of calories in proportion to their weight (TABLE 2). From the calculations in the table it can be seen that the conversion of glucose to tristearin would involve the loss of a considerable quantity of oxygen and would require an expenditure of energy that would necessitate the combustion of almost 30 per cent of glucose in excess of that actually required to form the structure of the fat.

TABLE 2

Tristearin ($C_{57}H_{110}O_6$)	1 gram = 9.3 cal.
Glucose ($C_6H_{12}O_6$)	1 gram = 3.8 cal.
To provide:	
C of 1 mole of tristearin	= C of 9.5 moles of glucose
1 mole of tristearin	= 8270 cal.
9.5 moles of glucose	= 6498 cal.
2.6 moles of glucose	= 1772 cal.

As a means of storing fuel, fat has peculiar advantages. A given weight of fat contains 9.3/4.1 = 2.3 times as many calories as an equal weight of glycogen or protein. The latter two, moreover, must be held in solution by about three times their weight of water, while fat is insoluble and requires no water. In terms of tissue or food, therefore, nine calories of fat occupy the same space or weight as one calorie of carbohydrate or protein. This constitutes the main problem of obesity. While fat conceals itself so readily in the food, it can be removed from the body only with great difficulty. With a deficit of 700 calories per day, it will take almost a year to lose 50 lb. of fat.

It was long believed that formation of fat from carbohydrate was a relatively rare process, utilized solely for the storage of surplus carbohydrate, observed only in gluttons and in fattening hogs. It is now recognized that it is continuously active, that probably, in the course of the day, a major proportion of the carbohydrate consumed is first converted to fat. The amount of glycogen, the only endogenous reserve of carbohydrate, is small and, under ordinary circumstances, relatively constant. The carbohydrate eaten at meals and not immediately consumed cannot be stored entirely as glycogen and expended between meals as carbohydrate. The major portion is probably converted to fat which is then burned.

A fatty acid appears first to be broken down into 2-carbon compounds in an explosive fashion, much as glycogen is broken down to glucose phosphate (FIGURE 7). In the liver, these 2-carbon fragments may again be coupled to form the 4-carbon compounds, acetoacetic and B-hydroxybutyric acids, which are conveyed to the tissues where they are oxidized. This process is exaggerated in starvation and when no exogenous carbohydrate is taken. It is further exaggerated when the ability to burn carbohydrate is impaired. This does not appear to be, as was once believed, the chief route for the combustion of fat. Fatty acids may be broken down in the tissues into 2-carbon compounds that are burned directly. It is the 2-carbon fragments derived from carbohydrate, which were mentioned earlier, that seem to be used for the formation of fat, the energy for the conversion being derived from combustion of a proportion of them. The 2-carbon fragments derived from fat seem to differ from those derived from carbohydrate, though both are ordinarily consumed in the Krebs combustion device. There is a large

Stearic acid, $C_{18}H_{36}O_2$ $\longrightarrow$ 9(2-carbon compounds)

Route 1 (Ketosis)

2(2-carbon compounds) = (4-carbon compound) → Burned to $CO_2 + H_2O$
acetoacetic acid
β-hydroxybutyric acid

Liver *Tissues*

Route 2 (Direct combustion)

2-carbon compounds $\longrightarrow$ Burned to $CO_2 + H_2O$

Tissues

FIGURE 7

body of evidence that the path from carbohydrate to fat is not freely and directly reversible.

In an attempt to integrate the metabolism of the three foodstuffs, certain simplifications must be made that involve some symbolism (FIGURE 8). For

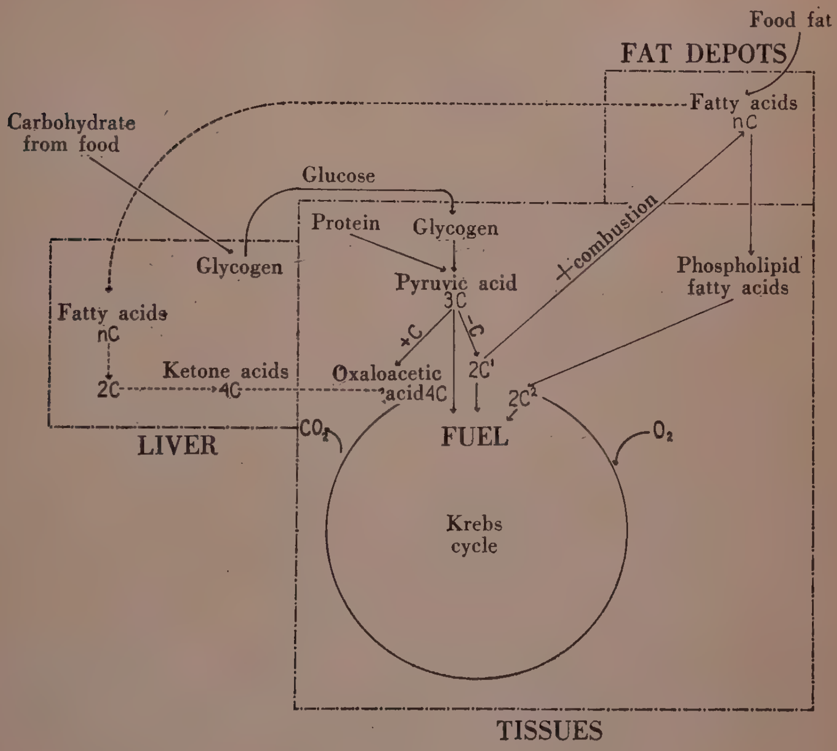


FIGURE 8.

these purposes, the body may be divided into three compartments: the general tissues, the liver, and the fat depots. The functions of the liver with respect to the elaboration of protein, production of urea, rearrangement of lipids, *etc.*, are neglected, though their importance is recognized. Only those functions immediately pertinent to the production of energy, which are performed through the Krebs cycle, are considered. This cycle, indicated by the circle in the tissue compartment, takes up oxygen and gives off CO_2 and water in the combustion of appropriate fuel that is fed to it through the top of the burner. In order that fuel may be burned, the machinery must be kept intact—that is, the 4-carbon compound, oxaloacetic acid, must be replenished. Glycogen of the liver is formed from the food and conveyed as glucose to the tissues, where it is again converted to glycogen. This is broken down to the 3-carbon compound, pyruvic acid, which has the capacity both to replenish oxaloacetic acid and to serve as fuel. With an adequate amount of pyruvic acid and intact reactions, therefore, the whole system will run without further assistance. The supply of pyruvic acid is supplemented continuously by protein in proportion to the quantity of protein catabolized. Pyruvic acid not required to replenish oxaloacetic acid or to supply fuel immediately is represented as forming 2-carbon groups, 2-C^1, which are used for the formation of fatty acids which, with fat derived from food, are deposited in the fat depots. This formation of fat demands energy which is secured by combustion of a proportion of the 2-C^1 fragments, which can be burned in the Krebs cycle but cannot be used to replenish oxaloacetic acid. From the fat depots fatty acids are conveyed to the phospholipids of the tissues. When they are needed for combustion, these are also broken down to 2-carbon groups, 2-C^2, which, like 2-C^1 from carbohydrate, can be burned but cannot form oxaloacetic acid. There is an alternate, less-used path, indicated by broken lines, by which fatty acids are conveyed to the liver. There they are broken into 2-carbon fragments which are immediately coupled to form 4-carbon groups, acetoacetic and B-hydroxybutyric acids which can be used to replace oxaloacetic acid, thereby enabling the 2-carbon groups from the phospholipids to be burned in the tissues. The ketone acids are not, however, utilized as efficiently as pyruvic acid is. The interplay of the foodstuffs cannot yet be defined with the precision that this diagram suggests, but the principles suggested by the diagram are consistent with known chemical reactions and with physiologic and pathologic phenomena.

If an individual is given no protein, but large amounts of carbohydrate and fat, the metabolism of protein is reduced to a minimum, and none is wasted for energy production. If the individual is given no food or no preformed carbohydrate to form pyruvic acid, the catabolism of protein increases, fat is mobilized to the liver, and the formation of ketone bodies increases. Both ketosis and destruction of protein are not merely aimed to provide fuel, but to take over the operative functions of carbohydrate, because the administration of as little as 100 grams of carbohydrate a day, altogether inadequate for the caloric needs, will abolish ketosis and prevent excessive wastage of protein. Ketosis, the provision from fat of substitutes for operative necessities usually derived from carbohydrate, may be regarded as an expedient to reduce the destruction of protein.

If the ability to burn carbohydrate is reduced to a minimum by removal of the pancreas, the machinery of the Krebs cycle continues, the fuel consumed is changed. The respiratory quotient of muscle from the diabetic animal approaches 0.70, indicating that it is deriving almost all its energy from fat. At just what points the chains of reactions are broken by the absence of insulin is not certain, but some of the direct consequences of the breaks are quite clear. One of the most important is the inability to form fat from carbohydrate. The far-reaching implications of this discovery can not be considered in this paper. In the diabetic, the formation of pyruvic acid is also impaired. In a futile effort to break through this obstruction to the maintenance of the Krebs cycle, the destruction of protein is increased. Effective relief is afforded by fat which is mobilized in large quantities from the depots and shipped over the broken-lined path to the liver, where it is broken down to provide ketone acids which can be used to form oxaloacetic acid, thereby enabling the Krebs cycle to continue and to burn the 2-carbon compounds derived from fat. Under these circumstances, fat, virtually unsupported, sustains energy production and the operative functions usually carried by carbohydrate. Although this substitution enables the subject to survive for a time, it involves the serious disadvantages of ketosis and resultant acidosis.

In the continuing metabolism, fat has achieved a novel position of importance. Except for the essential fatty acids, which have a purely operative role, fat is not altogether a separate foodstuff. It is equally an intermediary compound in the metabolism of carbohydrate. The metabolism of the two foodstuffs should no longer be categorically separated. The glucose-fed animal, so dear to physiologists and biochemists, is no longer what it used to be. Glycogen has already fallen far from the high estate it enjoyed in the reign of Hill and Meyerhoff, when it was the sole fuel of muscle. It is possible that it is now to be displaced from its position as the chief source of continuing energy. Under ordinary conditions, an adult male does not develop ketosis of any important degree until he has starved 48 hours or more, although the glycogen in his body could supply his energy requirements for only a fraction of this time. After an overnight fast, three-fifths of the energy production is sustained by fat. If it were not, the glycogen stores would be entirely exhausted. When there is not a continuous supply of exogenous carbohydrate, the endogenous supply is used with increasing economy as it becomes depleted. What little remains is reserved for essential operative purposes.

The hormones have received scant consideration because (1) the time allotted does not permit their inclusion, and (a) because their positions in the system and their modes of action are as yet quite undefined. In spite of the emotional plane to which they have been elevated, they do not occupy so fundamental a position in the metabolic system as the enzymes do. They probably control the speed, direction, and organization of the enzyme systems. It is through a more complete understanding of the latter that the true roles of the hormones are most likely to be elucidated.

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